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Recognition and Management of Pesticide Poisonings. Fourth Edition

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Abstract: The fourth edition of Recognition and Management of Pesticide Poisonings is an update and expansion of the 1982 third edition. The purpose of the fourth edition is to provide health professionals with recently available information on the health hazards of pesticides currently in use, and current consensus recommendations for management of poisonings and injuries caused by them. The book deals almost entirely with short-term (acute) harmful effects of pesticides.

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Recognition and Management of Pesticide Poisonings

Fourth Edition

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RECOGNITION AND MANAGEMENT OF PESTICIDE POISONINGS

Fourth Edition

Donald P. Morgan, M.D., Ph.D.*
1989

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Introduction

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This fourth edition of *Recognition and Management of Pesticide Poisonings* is an update and expansion of the 1982 third edition. The series, from 1973, has been sponsored by the Office of Pesticide Programs of the United States Environmental Protection Agency.

There have been good reasons for updated editions. New pesticide products are introduced regularly whose hazard potentials are not generally known to health professionals. The accumulated "use experience" of formulators, applicators, and field workers provides an expanding basis for judging safety or identifying hazards of old and new pesticides. Major episodes of adverse health effects reported in medical and scientific periodicals need to be taken into account. This literature also contributes importantly to improved understanding of toxic mechanisms. Finally, clinical toxicology is a dynamic field of medicine wherein new treatment methods are developed regularly and the effectiveness of old as well as new modalities undergoes constant critical review. The purpose of the fourth edition is to provide health professionals with recently available information on the health hazards of pesticides currently in use, and current consensus recommendations for management of poisonings and injuries caused by them.

All persons familiar with the clinical toxicology of pesticides agree that prevention of poisoning remains a much surer path to safety and health than reliance on treatment. In addition to the inherent toxic hazards of pesticides, none of the procedures or drugs used in treating poisonings are risk-free. In fact, many antidotes are plainly "toxic" in their own right, and such apparently simple procedures as gastric intubation incur substantial risk. The clinical toxicologist must often weigh the hazards of various courses of action—sometimes including no treatment at all—against the risks of various interventions, such as emptying the stomach, catharsis, giving intravenous fluids, or administering an antidote (when there is one). Management decisions have to be made promptly and, as often as not, on the basis of limited and scientifically insecure information. The complex circumstances of human poisonings rarely allow precise comparisons of alternative managements. In no sense, then, are the treatment recommendations in this book infallible guides to successful outcomes. They are no more than consensus judgments of the best available management options.

The book deals almost entirely with short-term (acute) harmful effects of pesticides. Although obviously important, the subject of chronic effects is too complex to deal with exhaustively in a manual designed as guidance for emergency management. Nonetheless, appropriate treatment of serious exposures to pesticides represents one important step in avoiding chronic as well as acute disease.

The amount of pesticide absorbed is a critical factor in making treatment decisions, and estimation of dosage in many circumstances of pesticide exposure remains difficult. The terms "small amount" and "large amount" used in this book are obviously ambiguous, but the quality of exposure information obtainable rarely justifies more specific terminology. The circumstances of exposure are sometimes a rough guide. Exposure to spray drift properly diluted for field application is not likely to convey a large dose unless exposure has been prolonged. Spills of concentrated technical material onto the skin or clothing may well represent a large dose of pesticide unless the contamination is promptly removed. Brief dermal exposure to foliage residues of cholinesterase-inhibiting pesticides is not likely to lead to poisoning, but prolonged exposures may well do so. Except in children, accidental pesticide ingestions are likely to be spat out or vomited, but suicidal ingestions almost always involve "large amounts," requiring the most aggressive management. Ingestions of pesticides by children are the most difficult to evaluate. The therapist usually must base his management on "worst case" assumptions of dosage. Childhood poisonings are still further complicated by the greater vulnerability of the very young (small body size), not only to pesticides themselves, but to the drugs and treatment procedures that must be used to limit the severity of poisoning.

The need to protect the airway from aspiration of vomitus cannot be over-emphasized. Death has occasionally resulted from this complication, even following ingestions of substances having relatively low toxic potential. In poisonings by agents which depress central nervous system function or cause convulsions, early placement of a cuffed endotracheal tube (even when this requires light general anesthesia) may be life-saving. Induced emesis is usually safe in alert patients, but great care must be taken in poisonings by neurotoxic agents that the airway is still protected when vomiting occurs. Maintenance of adequate pulmonary gas exchange is another essential element of poisoning management that deserves constant reemphasis.

Gastric intubation, with aspiration and lavage, remains a useful method for removing poisons from the stomach shortly after they have been swallowed, but the time after ingestion during which lavage is likely to be beneficial is shorter than many clinical toxicologists have thought. Rarely are significant amounts of swallowed toxicants recovered more than a few hours after ingestion, and, in many instances, the bulk of swallowed material passes into the duodenum and beyond in 15-30 minutes.

Full advantage should be taken of new highly adsorbent charcoals that are effective in binding some pesticides in the gut. Unfortunately, charcoal does not adsorb all pesticides, and its efficiency against many of them is not known. Because administration of charcoal is rarely followed by serious complications, its use is generally recommended if there is some likelihood that it will act beneficially. Sorbitol is an effective cathartic which somewhat reduces the distastefulness of charcoal and does not impair its adsorbency. The only problems attending use of sorbitol are those inherent in catharsis itself: dehydration and electrolyte disturbances, particularly in children.

In poisonings caused by large intakes of pesticide, hemodialysis and hemoperfusion over adsorbents continue to be tested as methods for reducing body burdens. Against some toxicants, these procedures are valuable. Overall effectiveness appears to depend not only on efficiency of clearance from the blood, but also on the mobility of toxicant already distributed to tissue cells before the extracorporeal blood-purification procedure is started. The critical determinant of success in using these systems may well be the speed with which they can be put into operation before tissue-damaging stores of toxicant have accumulated.

There remains a need for systematic reporting of pesticide poisonings to a central agency so that accurate statistics describing the frequency and circumstances of poisoning can be compiled, and efforts to limit these occurrences can be properly directed. It is realized that in recent years there has been a tragic increase in the use of pesticides as instruments of suicide and even homicide, particularly in the developing countries. Producers are now devoting considerable effort to modifications in formulation and packaging that will deter these misuses. This work is important because suicidal ingestions are by far the most difficult pesticide poisonings to treat successfully.

Among persons who encounter pesticides in the course of their occupational activities, dermal injuries, rather than systemic poisonings are the most common adverse effects.

An effort has been made to format this book for quick reference by thorough indexing and minimal references to other pages or chapters. However, some procedures are commonly used in treating poisonings by many different agents and it is not practical to repeat these protocols in every chapter. Methods for limiting toxicant absorption from the gastrointestinal tract are described in Chapter 1, TREATMENT, Section 6 (page 8). Control of convulsions is discussed in Chapter 3, TREATMENT, Section 4 (page 21). Management of pulmonary edema is considered in Chapter 14, TREATMENT, Section 4 (page 139). These sections have been referenced in several other chapters.

The contents of this book have been derived from many sources: published texts, current medical, toxicologic, and pesticide product literature, valuable instructional materials from the Iowa Poison Control Center, and direct communications with experts having knowledge of clinical toxicology in general and pesticide toxicology in particular. A list of the major text sources follows this introduction.

Critical reviews of draft material by experts in clinical toxicology have provided the real strength of this publication. Reviewers include:

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In addition to the expert reviewers, many individuals have contributed their time and skill to this fourth edition. Jerome M. Blondell, biostatistician for the Health Effects Division, Office of Pesticide Programs, United States Environmental Protection Agency, has supervised the review process, accomplished the indexing, and overseen the process of publication. The principal author is indebted to Mrs. Carol Hradek for skillful editorial assistance, to Ms. Joan McLaughlin, and to others of the secretarial staff of the Division of Occupational and Environmental Health, Department of Preventive Medicine and Environmental Health, The University of Iowa College of Medicine, for typing the manuscript.

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Fifth Edition
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with assistance of Jeannette E. Braddock
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Macmillan Publishing Company, New York, NY 1986

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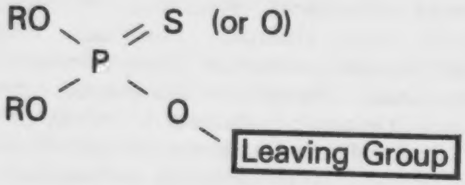
Fay M. Martin, and John T. Ensminger
Oak Ridge National Laboratory 1980

CHAPTER 1

ORGANOPHOSPHATE INSECTICIDES

GENERAL CHEMICAL STRUCTURE



R is usually either ethyl or methyl. Phosphonates contain an alkyl (R-) in place of one alkoxy group (RO-).

COMMERCIAL PRODUCTS

Highly toxic[*]: tetraethyl pyrophosphate (TEPP), dimefox (Hanane, Pestox XIV), phorate (Thimet, Rampart, AASTAR), disulfoton[+] (Disyston), fensulfothion (Dasanit), demeton[+] (Systox), terbufos (Counter, Contraven), mevinphos (Phosdrin, Duraphos), ethyl parathion (E605, Parathion, Thiophos), azinphos-methyl (Guthion, Gusathion), fosthietan (Nem-A-Tak), chlormephos (Dotan), sulfotep (Thiotepp, Bladafum, Dithione), carbophenothion (Trithion), chlorthiophos (Celathion), fonofos (Dyfonate, N-2790), prothoate[+] (Fac), fenamiphos (Nemacur), phosfolan[+] (Cyolane, Cylan), methyl parathion (E 601, Penncap-M), schradan (OMPA), mephosfolan[+] (Cytrolane), chlorfenvinphos (Apachlor, Birlane), coumaphos (Co-Ral, Asuntol), phosphamidon (Dimecron), methamidophos (Monitor), dicrotophos (Bidrin), monocrotophos (Azodrin), methidathion (Supracide, Ultracide), EPN, isofenphos (Amaze, Oftanol), endothion, bomyl (Swat), famphur (Famfos, Bo-Ana, Bash), fenophosphon (trichloronate, Agritox), dialifor (Torak), cyanofenphos (Surecide), dioxathion (Delnav), mipafox (Isopestox, Pestox XV).

Moderately toxic[*]: bromophos-ethyl (Nexagan), leptophos (Phosvel), dichlorvos (DDVP, Vapona), ethoprop (Mocap), demeton-S-methyl[+] (Duratox, Metasystox (i)), triazophos (Hostathion), oxydemeton-methyl[+] (Metasystox-R), quinalphos (Bayrusil), ethion (Ethanox), chlorpyrifos (Dursban, Lorsban, Brodan), edifenphos, oxydeprofos[+] (Metasystox-S), sulprofos (Bolstar, Helothion), isoxathion (E-48, Karphos), propetamphos (Safrotin), phosalone (Zolone), thiometon (Ekatin), heptenophos (Hostaquick), crotoxyphos (Ciodrin, Cypona), phosmet (Imidan, Prolate), trichlorfon (Dylox, Dipterex, Proxol, Neguvon), cythioate (Proban, Cyflee), phencapton (G 28029), pirimiphos-ethyl (Primicid), DEF (De-Green, E-Z-Off D), methyl trithion, dimethoate (Cygon, DeFend), fenthion (mercaptophos, Entex, Baytex, Tiguvon), dichlofenthion (VC-13 Nemacide), bensulide (Betasan, Prefar), EPBP (S-Seven), diazinon (Spectracide), profenofos (Curacron), formothion (Anthio), pyrazophos (Afugan, Curamil), naled (Dibrom), phenthoate (dimephenthoate, Phenthoate), IBP (Kitazin), cyanophos (Cyanox), crufomate (Ruelene), fenitrothion (Accothion, Agrothion, Sumithion), pyridaphenthion (Ofunack), acephate (Orthene), malathion (Cythion), ronnel (fenchlorphos, Korlan), etrimfos (Ekamet), phoxim (Baythion), merphos (Folex, Easy off-D), pirimiphos-methyl (Actellic), iodofenphos (Nuvanol-N), chlorphoxim (Baythion-C), propyl thiopyrophosphate (Aspon), bromophos (Nexion), tetrachlorvinphos (Gardona, Appex, Stirofos), temephos (Abate, Abathion).

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[*] Compounds are listed approximately in order of descending toxicity. "Highly toxic" organophosphates have listed oral LD_{50} values (rat) less than 50 mg/kg; "moderately toxic" agents have LD_{50} values in excess of 50 mg/kg.

[+] These organophosphates are systemic; they are taken up by the plant and translocated into foliage and sometimes into the fruit.

TOXICOLOGY

Organophosphates poison insects and mammals primarily by phosphorylation of the acetylcholinesterase enzyme (AChE) at nerve endings. The enzyme is critical to normal control of nerve impulse transmission from nerve fibers to muscle and gland cells, and also to other nerve cells in autonomic ganglia and in the brain. Some critical proportion of the tissue enzyme mass must be inactivated by phosphorylation before symptoms and signs of poisoning become manifest. At sufficient dosage, loss of enzyme function allows accumulation of acetylcholine (ACh, the impulse-transmitting substance) at cholinergic neuroeffector junctions (muscarinic effects), at skeletal nerve-muscle junctions and autonomic ganglia (nicotinic effects), and in the brain. At cholinergic nerve junctions with smooth muscle and gland cells, high ACh concentration causes muscle contraction and secretion, respectively. At skeletal muscle junctions, excess ACh may be excitatory (cause muscle twitching), but may also weaken or paralyze the cell by depolarizing the end-plate. In the brain, high ACh concentrations cause sensory and behavioral disturbances, incoordination and depressed motor function. Depression of respiration and pulmonary edema are the usual causes of death from organophosphate poisoning. Recovery depends ultimately on generation of new enzyme in all critical tissues.

Organophosphates are efficiently absorbed by inhalation, ingestion, and skin penetration. To a degree, the occurrence of poisoning depends on the rate at which the pesticide is absorbed. Breakdown occurs chiefly by hydrolysis in the liver; rates of hydrolysis vary widely from one compound to another. In the case of certain organophosphates whose breakdown is relatively slow, significant temporary storage in body fat may occur.

Many organophosphates readily undergo conversion from -thions (P=S) to -oxons (P=O). Conversion occurs in the environment under the influence of oxygen and light, and, in the body, chiefly by the action of liver microsomes. -Oxons are much more toxic than -thions, but -oxons break down more readily than -thions. Ultimately, both -thions and -oxons are hydrolyzed at the ester linkage, yielding alkyl phosphates and leaving groups. These are of relatively low toxicity. They are either excreted or further transformed in the body before excretion.

Within one to two days of initial organophosphate binding to acetylcholinesterase, some phosphorylated acetylcholinesterase enzyme can be de-phosphorylated (reactivated) by the oxime antidote pralidoxime. As time progresses, the enzyme-phosphoryl bond is strengthened by loss of one alkyl group from the phosphoryl adduct. Pralidoxime reactivation is thereafter no longer possible ("aging").

Rarely, certain organophosphates have caused a different kind of neurotoxicity consisting of damage to the axons of peripheral and central nerves and associated with inhibition of "neurotoxic esterase" (NTE). Manifestations have been chiefly weakness or paralysis and paresthesia of the extremities, predominantly the legs, persistent for weeks to years. Most of these rare occurrences have followed (8–21 days) an acute poisoning episode of the anticholinesterase type, but some have not been preceded by acute poisoning. Only a few of the many organophosphates used as pesticides have been implicated as causes of delayed neuropathy in humans. EPA guidelines require that organophosphate and carbamate compounds which are candidate pesticides be tested in susceptible animal species for this neurotoxic property.

Other specific properties of individual organophosphates may render them more hazardous than basic toxicity data suggest. By-products can develop in long-stored malathion which strongly inhibit the hepatic enzymes operative in malathion degradation, thus enhancing its toxicity. Certain organophosphates are exceptionally prone to storage in fat tissue, prolonging the need for antidote as stored pesticide is released back into the circulation. Animal studies have demonstrated potentiation of effect when two or more organophosphates are absorbed simultaneously: enzymes critical to the degradation of one are inhibited by the other. Whether this interaction is a significant factor in human poisonings is not known.

SYMPTOMS AND SIGNS OF POISONING

Symptoms of acute organophosphate poisoning develop during exposure, or within 12 hours (nearly always within 4 hours) of contact. The most commonly reported early symptoms are **HEADACHE, NAUSEA,** and **DIZZINESS.** Anxiety and restlessness are prominent. Worsening of the poisoned state is manifest as **MUSCLE TWITCHING, WEAK-**

NESS, tremor, incoordination, vomiting, abdominal cramps, and diarrhea. **HYPERSECRETION** is often prominent: sweating, salivation, tearing, rhinorrhea, and bronchorrhea. Blurred and/or dark vision may be reported, and **MIOSIS** is often a helpful diagnostic sign. Tightness in the chest, wheezing, and productive cough may progress to frank **PULMONARY EDEMA**. Bradycardia may progress to sinus arrest, or may be superseded by tachycardia and hypertension from nicotinic (sympathetic ganglia) stimulation. Toxic psychosis, manifest as confusion or bizarre behavior, has been misdiagnosed as acute alcoholism. Toxic myocardiopathy has been a prominent feature of some severe organophosphate poisonings. Unconsciousness, incontinence, convulsions, and depression of respiratory drive signify a life-threatening severity of poisoning.

Repeated absorption of organophosphate at significant dosage, but in amounts not sufficient to cause acute poisoning, may cause persistent anorexia, weakness, and malaise.

Some recently reported cases of organophosphate poisoning, mostly from suicidal ingestion of large quantities, have been characterized by prolonged (1-3 weeks) paralysis of muscles of the head, neck, limbs, and thorax, commencing one to four days following apparent resolution of acute cholinergic manifestations. Continuous mechanical support of pulmonary ventilation was necessary to sustain life in these cases.

CONFIRMATION OF ORGANOPHOSPHATE ABSORPTION

CAUTION: If there are strong clinical indications of acute organophosphate poisoning, treat patient immediately. **DO NOT WAIT** for laboratory confirmation.

Depressions of plasma pseudocholinesterase and/or RBC acetylcholinesterase enzyme activities are generally available biochemical indicators of excessive organophosphate absorption. A minimum amount of organophosphate must be absorbed to depress blood cholinesterase activities, but enzyme activities are lowered by dosages considerably less than are required to cause symptomatic poisoning. The enzyme depression is usually apparent within a few minutes or hours of significant absorption of organophosphate. Depression of the plasma enzyme generally persists several days to a few weeks; the RBC enzyme activity may not reach its minimum for several days, and usually remains depressed longer, sometimes 1-3 months, until new enzyme replaces that inactivated by organophosphate. Table 1 lists **APPROXIMATE LOWER LIMITS OF NORMAL FOR PLASMA AND RBC CHOLINESTERASE ACTIVITIES** of human blood, measured by several methods. **LOWER LEVELS** usually indicate excessive absorption of a cholinesterase-inhibiting chemical. Whenever possible, comparison of the test sample value with a pre-exposure value offers the best confirmation of organophosphate absorption. A cholinesterase depression of 25% or more is generally regarded as evidence of excessive absorption.

TABLE 1. *Approximate Lower Limits of Normal Plasma and Red Cell Cholinesterase Activities in Humans**

METHOD	PLASMA	RBC	WHOLE BLOOD	UNITS
pH (Michel)	0.45	0.55		ΔpH per ml per hr
pH Stat (Nabb-Whitfield)	2.3	8.0		μM per ml per min
BMC Reagent Set (Ellman-Boehringer)	1875		3000	mU per ml per min
Dupont ACA	<8			Units per ml
Garry-Routh (Micro)			Male 7.8 Female 5.8	μM-SH per 3 ml per min
Technicon	2.0	8.0		μM per ml per min

* Because measurement technique varies among laboratories, more accurate estimates of minimum normal values are usually provided by individual laboratories.

In certain conditions, the activities of plasma and RBC cholinesterase are depressed in the absence of chemical inhibition. About 3% of individuals have a genetically determined low level of plasma pseudocholinesterase. These persons are particularly vulnerable to the action of the muscle-paralyzing drug succinylcholine, often administered to surgical patients. They may be unusually sensitive to organophosphate toxicity, although this has not been proven. Patients with advanced liver disease, malnutrition, chronic alcoholism, and dermatomyositis exhibit low plasma cholinesterase activities. A number of toxicants, notably carbon disulfide, benzalkonium salts, organic mercury compounds, ciguatoxins, and solanines may reduce plasma pseudocholinesterase activity. Early pregnancy and birth control pills may also cause some depression. The RBC acetylcholinesterase is less likely than the plasma enzyme to be affected by factors other than organophosphates. It is reduced, however, in certain rare conditions that damage the red cell membrane, such as the hemolytic anemias.

The alkyl phosphates and phenols to which organophosphates are hydrolyzed in the body can often be detected in the urine during pesticide absorption and up to about 48 hours thereafter. These analyses are sometimes useful in identifying the actual pesticide to which workers have been exposed. Urinary alkyl phosphate and phenol analyses can demonstrate organophosphate absorption at lower dosages than those required to depress cholinesterase activities and at much lower dosages than those required to produce symptoms and signs.

Detection of intact organophosphates in the blood is usually not possible except during or soon after absorption of substantial amounts. In general, organophosphates do not remain unhydrolyzed in the blood more than a few minutes or hours, unless the quantity absorbed is large or the hydrolyzing liver enzymes are inhibited.

TREATMENT OF ORGANOPHOSPHATE POISONING

CAUTION: Persons attending the victim should avoid direct contact with heavily contaminated clothing and vomitus. Wear rubber gloves while washing pesticide from skin and hair.

1. Insure that a **CLEAR AIRWAY** exists by aspiration of secretions, if necessary. Administer **OXYGEN** by mechanically assisted pulmonary ventilation if respiration is depressed. Improve tissue oxygenation as much as possible before administering atropine, so as to minimize the risk of ventricular fibrillation.

   In **SEVERE** poisonings, it may be necessary to support pulmonary ventilation mechanically for several days.
2. Administer **ATROPINE SULFATE** intravenously, or intramuscularly if intravenous injection is not possible.

   The objective of atropine antidotal therapy is to antagonize the effects of excessive concentrations of acetylcholine at end-organs having muscarinic receptors. Depending on the severity of poisoning, doses of atropine ranging from small to very large may be required. Atropine does not reactivate the cholinesterase enzyme or accelerate disposition of organophosphate. Recrudescence of poisoning may occur if tissue concentrations of organophosphate remain high when the effect of atropine wears off. Atropine is effective against muscarinic manifestations, but it is ineffective against nicotinic actions, specifically muscle weakness and twitching, and respiratory depression. Despite these limitations, atropine is often a lifesaving agent in organophosphate poisonings. Favorable response to a test dose of atropine (1 mg in adults, 0.01 mg/kg in children under 12 years) can help differentiate poisoning by anticholinesterase agents from other conditions.

   In **MODERATELY SEVERE** poisoning (hypersecretion and other end-organ manifestations without central nervous system depression) the following dosage schedules have proven effective:

   Dosage of **ATROPINE:**

   Adults and children over 12 years: 0.4–2.0 mg repeated every 15 minutes until atropinization is achieved: flushing, dry mouth, dilated pupils, and tachycardia (pulse of 140 per minute). Maintain atropinization by repeated doses for 2–12 hours or longer depending on severity of poisoning. Rales in the lung bases nearly always indicate inadequate atropinization. Miosis, nausea, bradycardia, and other cholinergic manifestations also signal the need for more atropine.

   Children under 12 years: 0.05 mg/kg body weight, repeated every 15 minutes until atropinization is achieved. Maintain atropinization with repeated dosage of 0.02–0.05 mg/kg body weight.

SEVERELY POISONED individuals may exhibit remarkable tolerance to atropine; two or more times the dosages suggested above may be needed. The dose of atropine may be increased and the dosing interval decreased as needed to control symptoms. Continuous intravenous infusion of atropine may be necessary when atropine requirements are massive. **REVERSAL OF MUSCARINIC SYMPTOMS AND SIGNS**, not an arbitrary dose limit, is the desired end-point. Preservative-free atropine products should be used whenever possible.

Note: Persons not poisoned or only slightly poisoned by organophosphates may develop signs of atropine toxicity from such large doses: **FEVER**, muscle fibrillations, and delirium are the main signs of atropine toxicity. If these appear while the patient is fully atropinized, atropine administration should be discontinued, at least temporarily, while the severity of poisoning is reevaluated.

3. Draw a **BLOOD SAMPLE** (heparinized) for cholinesterase analysis before administration of pralidoxime, which tends to reverse the cholinesterase depression.
4. Administer **PRALIDOXIME** (Protopam, 2-PAM), a cholinesterase reactivator, in cases of severe poisoning by organophosphate pesticides in which respiratory depression, muscle weakness, and twitching are severe. When administered early (usually less than 48 hours after poisoning) pralidoxime relieves the nicotinic as well as the muscarinic effects of poisoning.

Note: Pralidoxime is of limited value, and may be hazardous, in poisonings by the cholinesterase-inhibiting carbamate compounds (see Chapter 2).

Dosage of **PRALIDOXIME:**

Adults and children over 12 years: 1.0–2.0 gm intravenously at no more than 0.2 gm per minute.

Children under 12 years: 20–50 mg/kg body weight (depending on severity of poisoning) intravenously, injecting no more than half the total dose per minute.

Dosage of pralidoxime may be repeated in 1–2 hours, then at 10–12 hour intervals if needed. In very severe poisonings, dosage rates may be doubled. Repeated doses of pralidoxime are usually required. In cases that involve continuing absorption of organophosphate (as after ingestion of a large amount), or continuing transfer of highly lipophilic organophosphate from fat into blood, it may be necessary to continue administration of pralidoxime for several days beyond the 48 hour post-exposure interval usually cited as the limit of its effectiveness.

Slow administration of pralidoxime is strongly recommended and may be achieved by administering the total dose in 250 ml 5% glucose solution over 30 minutes, or longer. Blood pressure should be monitored during administration because of the occasional occurrence of hypertensive crisis. Administration should be slowed or stopped if blood pressure rises to hazardous levels. Be prepared to assist pulmonary ventilation mechanically if respiration is depressed during or after pralidoxime administration.

If intravenous injection is not possible, pralidoxime may be given by deep intramuscular injection.

5. In patients who have been poisoned by organophosphate contamination of skin, clothing, hair, and/or eyes, **DECONTAMINATION MUST PROCEED CONCURRENTLY** with whatever resuscitative and antidotal measures are necessary to preserve life. Contamination of the eyes should be removed by flushing with copious amounts of clean water. If no symptoms are evident in a patient who remains alert and physically able, a prompt shower and shampoo may be appropriate, provided the patient is carefully observed to insure against sudden appearance of poisoning. If there are any indications of weakness, ataxia, or other neurologic impairment, clothing should be removed and a complete **BATH AND SHAMPOO** given while the victim is recumbent, using copious amounts of soap and water. Attendants should wear rubber gloves. Surgical green soap is excellent for this purpose, but ordinary soap is about as good. The possibility of pesticide sequestered under fingernails or in skin folds should not be overlooked. **CONTAMINATED CLOTHING** should be promptly bagged and not returned until it has been thoroughly laundered. Contaminated leather shoes should be discarded. The possibility that pesticide has contaminated the inside surfaces of gloves, boots, and headgear should be kept in mind.

6. **IF ORGANOPHOSPHATE HAS BEEN INGESTED** in quantity probably sufficient to cause poisoning, the stomach and intestine must be emptied.

   Because central nervous system depression may develop rapidly, gastric **LAVAGE** through a large bore orogastric tube, with rigorous protection of the airway, is probably preferable to emesis in nearly all cases of poisoning by ingested organophosphate. Effectiveness of lavage diminishes rapidly with the passage of time.

   A. Empty the stomach by **INTUBATION, ASPIRATION,** and **LAVAGE,** using a slurry of activated charcoal in isotonic saline (see below). Rigorous precautions must be taken to **PROTECT THE AIRWAY** from aspiration of regurgitated gastric contents:
      (a) If victim is unconscious or obtunded, insert a cuffed **ENDOTRACHEAL TUBE** prior to gastric intubation.
      (b) **KEEP VICTIM'S HEAD BELOW LEVEL OF STOMACH** during gastric intubation and lavage (Trendelenburg, or left lateral decubitus, with head of table tipped downward). Keep victim's head turned to the left.

(c) **ASPIRATE PHARYNX** as regularly as possible to remove gagged or vomited stomach contents.

B. After aspiration of stomach contents and lavage, instill **ACTIVATED CHARCOAL** ("preferably >3000" m^2 surface area per gm) together with a **CATHARTIC** in the charcoal slurry. Even though adsorption of organophosphates on charcoal is not very efficient, charcoal instillation may be of some value.

Dosage of **CHARCOAL** as an aqueous slurry:

Adults and children over 12 years: 50–100 gm in 300–800 ml water.

Children under 12 years: 15–30 gm in 100–300 ml water.

Dosage of **SORBITOL** (the preferred agent) added to charcoal slurry:

Adults and children over 12 years: 1.0–2.0 gm/kg body weight to a maximum of 150 gm per dose.

Children under 12 years: 1.0–1.5 gm/kg body weight to a maximum of 50 gm per dose.

Alternative cathartics that may be used instead are sodium or magnesium sulfate or citrate:

Dosage of **SODIUM** or **MAGNESIUM SULFATE:**

Adults and children over 12 years: 20–30 gm.

Children under 12 years: 250 mg/kg body weight.

Dosage of **MAGNESIUM CITRATE** solution:

Adults and children: 4 ml/kg body weight of proprietary solution, up to a maximum of 300 ml.

CAUTION: Do not instill fluid so rapidly that overloading of the stomach leads to vomiting or regurgitation. Serious electrolyte disturbances may follow catharsis, especially in young children. Monitor serum electrolytes regularly, including magnesium levels, if magnesium salts have been used.

C. If gastric aspiration and lavage is not performed due to delay in treatment, and if patient is fully alert, **ADMINISTER** doses of **CHARCOAL AND CATHARTIC ORALLY,** as indicated in 6.B. When sorbitol is given orally, it should be diluted with an equal volume of water to yield a 35% solution.

D. **SAVE** a sample of emesis or initial gastric washings for chemical analysis.

E. In some cases of organophosphate ingestion there may be benefit from **REPEATED ADMINISTRATION OF ACTIVATED CHARCOAL,** either by ingestion or stomach tube, at doses approximating those recommended in 6.B. above. While charcoal incurs little risk, repeated catharsis may cause serious dehydration and electrolyte depletion, especially in children. Cathartic should not be administered after a charcoal stool appears.

7. **OBSERVE PATIENT CLOSELY** for at least 72 hours (longer in cases of organophosphate ingestion) to insure that symptoms

(sweating, visual disturbances, vomiting, diarrhea, chest and abdominal distress, and sometimes **PULMONARY EDEMA**) do not recur as atropinization is withdrawn. In very severe poisonings by ingested organophosphates, particularly the more lipophilic and slowly hydrolyzed compounds, metabolic disposition of toxicant may require as many as 5–14 days. In some cases, this slow elimination may combine with profound cholinesterase inhibition to require atropinization for several days or even weeks. Rising levels of blood cholinesterase activity are a useful signal that atropine dosage can be tapered off by lengthening the intervals between doses. As dosage is reduced, the lung bases should be checked frequently for rales. If rales are heard, or if there is a return of miosis, bradycardia, sweating or other cholinergic signs, atropinization must be re-established promptly.

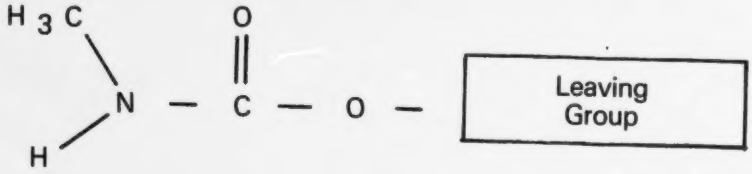
8. Particularly in poisonings by large ingested doses of organophosphate, **MONITOR PULMONARY VENTILATION** carefully, even after recovery from muscarinic symptomatology, to forestall respiratory failure. In some cases, respiratory failure has developed several days following organophosphate ingestion, and has persisted for days to weeks.
9. In severely poisoned patients, **MONITOR CARDIAC STATUS** by continuous ECG recording. Some organophosphates have significant cardiac toxicity.
10. Furosemide may be considered for relief of pulmonary edema if rales persist in the lungs even after full atropinization. It should not be used until the maximum benefit of atropine has been realized. Consult package insert for dosage and administration.
11. The following drugs are probably contraindicated in nearly all organophosphate poisoning cases: morphine, theophylline, phenothiazines, and reserpine. Adrenergic amines should be given only if there is a specific indication, such as marked hypotension.
12. Rarely, in severe organophosphate poisonings, **CONVULSIONS** occur despite therapy with atropine and pralidoxime. Insure that causes unrelated to pesticide toxicity are not responsible: head trauma, cerebral anoxia, or mixed poisoning. Drugs useful in controlling convulsions are discussed in Chapter 3, TREATMENT, Section 4, p. 21. The benzodiazepines diazepam or lorazepam are probably the agents of choice as initial therapy.
13. Persons who have been clinically poisoned by organophosphate pesticides should not be re-exposed to cholinesterase-inhibiting chemicals until symptoms and signs have resolved completely and blood cholinesterase activities have returned to at least 80 percent of pre-poisoning levels. If blood cholinesterase was not measured prior to poisoning, blood enzyme activities should reach at least minimum normal levels (Table 1) before the patient is returned to a pesticide-contaminated environment.

14. **DO NOT ADMINISTER ATROPINE OR PRALIDOXIME PROPHYLACTICALLY** to workers exposed to organophosphate pesticides. Prophylactic dosage with either atropine or pralidoxime may mask early signs and symptoms of organophosphate poisoning and thus allow the worker to continue exposure and possible progression to more severe poisoning. Atropine itself may enhance the health hazards of the agricultural work setting: impaired heat loss due to reduced sweating and impaired ability to operate mechanical equipment due to blurred vision (mydriasis).

CHAPTER 2

N-METHYL CARBAMATE INSECTICIDES

GENERAL CHEMICAL STRUCTURE



COMMERCIAL PRODUCTS

Highly toxic[*]: aldicarb[+] (Temik), oxamyl (Vydate L, DPX 1410), methiocarb (Mesurol, Draza), carbofuran (Furadan, Curaterr, Crisfuran), isolan (Primin), methomyl (Lannate, Nudrin, Lanox), formetanate (Carzol), aminocarb (Matacil), cloethocarb (Lance), bendiocarb (Ficam, Dycarb, Multamat, Niomil, Tattoo, Turcam).

Moderately toxic[*]: dioxacarb (Elocron, Famid), promecarb (Carbamult), bufencarb (metalkamate, Bux), propoxur (aprocarb, Baygon), trimethacarb (Landrin, Broot), pirimicarb (Pirimor, Abol, Aficida, Aphox, Fernos, Rapid), dimetan (Dimethan), carbaryl (Sevin, Dicarbam), isoprocarb (Etrofolan, MIPC).

TOXICOLOGY

The N-methyl carbamate esters cause reversible carbamylation of acetylcholinesterase enzyme, allowing accumulation of acetylcholine, the neuromediator substance, at parasympathetic neuroeffector junctions (muscarinic effects), at skeletal muscle myoneural junctions and autonomic ganglia (nicotinic effects), and in the brain (CNS effects). The carbamyl-acetylcholinesterase combination dissociates more readily than the phosphoryl-acetylcholinesterase complex produced by organophosphate compounds. This lability has several important consequences: 1) it tends to limit the duration of N-methyl carbamate poisonings, 2) it accounts for the greater span between symptom-producing and lethal doses than exists in the case of most organophosphate compounds, and 3) it frequently invalidates the measurement of blood cholinesterase activity as a diagnostic index of poisoning (see below). N-methyl carbamates are absorbed by inhalation and ingestion and some by skin penetration. Dermal absorption of particular compounds (notably carbofuran) is very slight. N-methyl carbamates are hydrolyzed enzymatically by the liver and the degradation products are excreted by the kidneys and the liver.

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[*] Compounds are listed approximately in order of descending toxicity. "Highly toxic" N-methyl carbamates have listed oral LD_{50} values (rat) less than 50 mg/kg body weight; "moderately toxic" agents have LD_{50} values in excess of 50 mg/kg.

[+] This pesticide is taken up by some plants into the foliage and sometimes into the fruit.

At cholinergic nerve junctions with smooth muscle and gland cells, high acetylcholine concentration causes muscle contraction and secretion, respectively. At skeletal muscle junctions, excess acetylcholine may be excitatory (cause muscle twitching), but may also weaken or paralyze the cell by depolarizing the end-plate. In the brain, elevated acetylcholine concentrations may cause sensory and behavioral disturbances, incoordination, and depressed motor function (rarely seizures), even though the N-methyl carbamates do not penetrate the central nervous system very efficiently. Depression of respiration combined with pulmonary edema is the usual cause of death from poisoning by N-methyl carbamate compounds.

SYMPTOMS AND SIGNS OF POISONING

MALAISE, MUSCLE WEAKNESS, DIZZINESS, and **SWEATING** are commonly reported early symptoms of poisoning. Headache, salivation, nausea, vomiting, abdominal pain, and diarrhea are often prominent. Miosis, incoordination, and slurred speech are reported. Dyspnea, bronchospasm, and chest tightness may eventuate in **PULMONARY EDEMA.** Blurred vision, muscle twitching, and spasms characterize some cases. Severe neurologic manifestations, including convulsions, are less common than in organophosphate poisonings. Bradycardia occurs infrequently. Poisonings by N-methyl carbamates tend to be of shorter duration than poisonings by organophosphates, but they are not easily differentiated from organophosphate poisoning in the acute phase in the absence of an accurate exposure history.

CONFIRMATION OF N-METHYL CARBAMATE ABSORPTION

Unless a substantial amount of N-methyl carbamate has been absorbed and a blood sample is taken within an hour or two, it is unlikely that blood cholinesterase activities will be found depressed. Even under the above circumstances, a rapid test for enzyme activity must be used to detect an effect, because enzyme reactivation occurs in vitro as well as in vivo. See Table 1 of Chapter 1 for methods of measurement of blood cholinesterase activities, if circumstances appear to warrant performance of the test.

Absorption of some N-methyl carbamates can be confirmed by analysis of urine for unique metabolites: alpha-naphthol from carbaryl, isopropoxyphenol from propoxur, carbofuran phenol from carbofuran, aldicarb sulfone and nitrile from aldicarb. Unfortunately, analyses for these excretion end-products are complex and not generally available.

TREATMENT OF N-METHYL CARBAMATE INSECTICIDE POISONING

CAUTION: Persons attending the victim should avoid direct contact with heavily contaminated clothing and vomitus. Wear rubber gloves while washing pesticide from skin and hair.

1. Insure that a **CLEAR AIRWAY** exists by aspiration of secretions, if necessary. Administer **OXYGEN** by mechanically assisted pulmonary ventilation as needed. Improve tissue oxygenation as much as possible before administering atropine, so as to minimize the risk of ventricular fibrillation. Support pulmonary ventilation mechanically as long as respiratory drive is depressed.
2. Administer **ATROPINE SULFATE** intravenously, or intramuscularly, if intravenous injection is not possible. The objective of atropine antidotal therapy is to antagonize the effects of excessive concentrations of acetylcholine at end-organs having muscarinic receptors. Depending on the severity of poisoning, doses of atropine ranging from small to very large may be required. Atropine does not reactivate the cholinesterase enzyme or accelerate excretion or breakdown of pesticide. Recrudescence of poisoning may occur if tissue concentrations of toxicant remain high when the effect of atropine wears off. Atropine is effective against muscarinic manifestations, but it is ineffective against nicotinic actions, specifically muscle weakness and twitching, and respiratory depression. Despite these limitations, atropine is often a lifesaving agent in N-methyl carbamate poisonings. Favorable response to a test dose of atropine (1 mg in adults, 0.01 mg/kg in children under 12 years) given intravenously can help differentiate poisoning by anticholinesterase agents from other conditions.

   In **MODERATELY SEVERE** poisoning (hypersecretion and other end-organ manifestations without central nervous system depression) the following dosage schedules have proven effective:

   Dosage of **ATROPINE:**

   Adults and children over 12 years: 0.4–2.0 mg repeated every 15 minutes until atropinization is achieved: tachycardia (pulse of 140 per minute), flushing, dry mouth, dilated pupils. Maintain atropinization by repeated doses for 2–12 hours or longer depending on severity of poisoning. Rales in the lung bases nearly always indicate inadequate atropinization. Miosis, nausea, bradycardia, and other cholinergic manifestations also signal the need for more atropine.

   Children under 12 years: 0.05 mg/kg body weight, repeated every 15 minutes until atropinization is achieved. Maintain atropinization with repeated doses of 0.02–0.05 mg/kg body weight.

SEVERELY POISONED individuals may exhibit remarkable tolerance to atropine; two or more times the dosages suggested above may be needed. Reversal of muscarinic manifestations, rather than a specific dosage, is the object of atropine therapy. However, prolonged intensive intravenous administration of atropine sometimes required in organophosphate poisonings is rarely needed in treating carbamate poisoning. **Note:** Persons not poisoned or only slightly poisoned by N-methyl carbamates may develop signs of atropine toxicity from such large doses. **FEVER,** muscle fibrillations, and delirium are the main signs of atropine toxicity. If these signs appear while the patient is fully atropinized, atropine administration should be discontinued, at least temporarily, while the severity of poisoning is reevaluated.

3. Save a **URINE SAMPLE** for metabolite analysis if there is need to identify the agent responsible for the poisoning. Also, urine metabolite measurement can be used to follow the progress of carbamate disposition.
4. Pralidoxime is probably of little value in N-methyl carbamate poisonings. Its use is usually unnecessary because atropine alone is effective, and in some cases of carbamate poisoning, pralidoxime administration has been followed by severe reactions, even sudden death. Both animal studies and experience in human poisonings **CONTRAINDICATE USE OF PRALIDOXIME IN CARBARYL POISONINGS.** In mixed poisonings involving organophosphates, or in poisonings by unidentified anticholinesterase agents which produce significant nicotinic effects, cautious administration of pralidoxime may have to be considered (see Chapter 1, TREATMENT, Section 4, p. 7).
5. In patients who have been poisoned by carbamate pesticide contamination of skin, clothing, hair, and/or eyes, **DECONTAMINATION MUST PROCEED CONCURRENTLY** with whatever resuscitative and antidotal measures are needed to preserve life. Contamination of the eyes should be removed by flushing with copious amounts of clean water. For asymptomatic individuals who are alert and physically able, a prompt shower and shampoo may be appropriate, provided the patient is carefully observed to insure against sudden appearance of poisoning. If there are any indications of weakness, ataxia, or other neurologic impairment, clothing should be removed and a complete bath and shampoo given while the victim is recumbent, using copious amounts of soap and water. Attendants should wear rubber gloves. Surgical green soap is excellent for this purpose, but ordinary soap is about as good. The possibility of pesticide sequestered under fingernails or in skin folds should not be overlooked. **CONTAMINATED CLOTHING** should be promptly removed, bagged, and

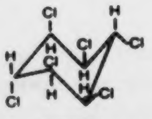
not returned until it has been thoroughly laundered. Contaminated leather shoes should be discarded. The possibility that pesticide has contaminated the inside surfaces of gloves, boots, and headgear should be kept in mind.

6. **IF N-METHYL CARBAMATE HAS BEEN INGESTED** in a quantity probably sufficient to cause poisoning, the stomach and intestine must be emptied, and measures taken to limit absorption from the gut. Procedures for accomplishing this are essentially the same as those used in organophosphate poisonings. See Chapter 1, TREATMENT, Section 6, p. 8.
7. **OBSERVE PATIENT CLOSELY** for at least 24 hours to insure that symptoms (sweating, visual disturbances, vomiting, diarrhea, chest and abdominal distress, and sometimes **PULMONARY EDEMA**) do not recur as atropinization is withdrawn. As the dosage of atropine is reduced over time, check the lung bases frequently for rales. If rales are heard, or if there is a return of miosis, sweating or other signs of poisoning, atropinization must be re-established promptly.
8. Furosemide may be considered for relief of pulmonary edema if rales persist in the lungs even after full atropinization. It should not be considered until the maximum effect of atropine has been achieved. Consult package insert for dosage and administration.
9. Particularly in poisonings by large doses of N-methyl carbamates, **MONITOR PULMONARY VENTILATION** carefully, even after recovery from muscarinic symptomatology, to forestall respiratory failure.
10. In severely poisoned patients, **MONITOR CARDIAC STATUS** by continuous ECG recording.
11. The following drugs are probably contraindicated in nearly all N-methyl carbamate poisoning cases: morphine, theophylline, phenothiazines, and reserpine. Adrenergic amines should be given only if there is a specific indication, such as marked hypotension.
12. Persons who have been clinically poisoned by N-methyl carbamate pesticides should not be re-exposed to cholinesterase-inhibiting chemicals until symptoms and signs have resolved completely.
13. **DO NOT ADMINISTER ATROPINE PROPHYLACTICALLY** to workers exposed to N-methyl carbamate pesticides. Prophylactic dosage may mask early symptoms and signs of carbamate poisoning and thus allow the worker to continue exposure and possible progression to more severe poisoning. Atropine itself may enhance the health hazards of the agricultural work setting: impaired heat loss due to reduced sweating and impaired ability to operate mechanical equipment due to blurred vision (mydriasis).

CHAPTER 3

SOLID ORGANOCHLORINE INSECTICIDES

CHEMICAL STRUCTURES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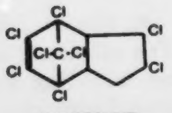
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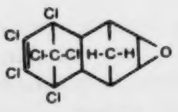
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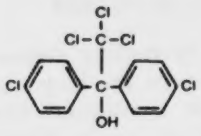
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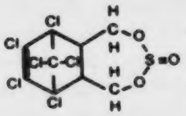
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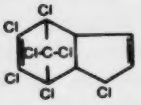
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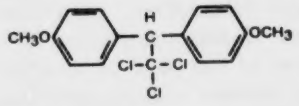
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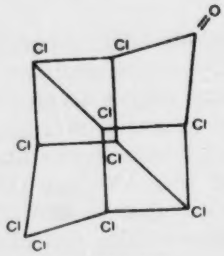
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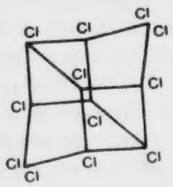
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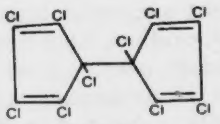

DIENOCHLOR

COMMERCIAL PRODUCTS

Endrin (Hexadrin), aldrin (Aldrite, Drinox), endosulfan (Thiodan), dieldrin (Dieldrite), toxaphene (Toxakil, Strobane-T), lindane (gamma BHC or HCH, Isotox), hexachlorocyclohexane (BHC), DDT (chlorophenothane), heptachlor (Heptagran), chlordecone (Kepone), terpene polychlorinates (Strobane), chlordane (Chlordan), dicofol (Kelthane), mirex (Dechlorane), methoxychlor (Marlate), dienochlor (Pentac), TDE (DDD, Rhothane), ethylan (Perthane).

The United States Environmental Protection Agency has sharply curtailed the availability of many organochlorines, particularly DDT, dieldrin, heptachlor, mirex, chlordecone, and chlordane. Others, however, are still the active ingredients of various home and garden products and some agricultural, structural, and environmental pest control products. Hexachlorobenzene is used as a seed protectant fungicide.

Technical hexachlorocyclohexane (misnamed benzene hexachloride, BHC) includes multiple stereoisomers; only the gamma isomer (lindane) is insecticidal. Lindane is the active ingredient of some pest control products used in the home and garden, on the farm, and in forestry and animal husbandry. It is also the active agent in the medicinal Kwell, used for human ectoparasitic disease.

TOXICOLOGY

In varying degrees, organochlorines are absorbed from the gut and also by the lung and across the skin. The efficiency of dermal absorption is variable. Hexachlorocyclohexane, including lindane, the cyclodienes (aldrin, dieldrin, endrin, chlordane, heptachlor) and endosulfan are efficiently absorbed across skin, while dermal absorption efficiencies of DDT, perthane, dicofol, methoxychlor, toxaphene, mirex, and kepone are substantially less. Gastrointestinal, and probably dermal, absorption of organochlorines is enhanced by fat and fat solvents. While most of the solid organochlorines are not highly volatile, pesticide-laden aerosol or dust particles trapped in respiratory mucous and subsequently swallowed may be vehicles leading to significant gastrointestinal absorption.

Following exposure to some organochlorines (notably DDT), a significant part of the absorbed dose is stored in fat tissue as the unchanged parent compound. Most organochlorines are in some degree dechlorinated, oxidized, then conjugated. The chief route of excretion is biliary, although nearly all organochlorines yield measurable urinary metabolites. Unfortunately, many of the unmetabolized pesticides are efficiently reabsorbed by the intestine (enterohepatic circulation) substantially retarding fecal excretion. Metabolic dispositions of DDT and DDE (a DDT degradation product), the beta isomer of hexachlorocyclohexane, dieldrin, heptachlor epoxide, mirex, and kepone tend to be slow, leading to storage in body fat. Storable lipophilic compounds are likely to be excreted in maternal milk.

Rapid metabolic dispositions of lindane, methoxychlor, dienochlor, endrin, chlorobenzilate, dicofol, toxaphene, perthane, and endosulfan reduce the likelihood that these organochlorines will be detected as residues in body fat, blood, or milk.

The cyclodiene aldrin is efficiently epoxidized in the body (and in the environment) to dieldrin. A similar biotransformation converts heptachlor to heptachlor epoxide. These conversions have little effect on toxicity of the parent compound. The epoxides are sometimes identified in body fat, blood, and milk.

Lindane is partially dechlorinated and oxidized following absorption, promptly yielding a series of conjugated chlorophenols and other oxidation products in the urine.

The chief toxic action of the organochlorine pesticides is on the nervous system, where these compounds interfere with fluxes of cations across nerve cell membranes, increasing neuronal irritability. This effect is manifest mainly as convulsions, sometimes limited to myoclonic jerking, but often expressed as violent seizures. Convulsions caused by the more slowly metabolized cyclodienes may recur over periods of several days. Convulsions may cause death by interfering with pulmonary gas exchange and by generating severe metabolic acidosis. Various disturbances of sensation, coordination, and mental function are also characteristic of acute organochlorine poisoning. High tissue concentrations of organochlorines increase myocardial irritability, predisposing to cardiac arrhythmias. When tissue organochlorine concentrations drop below threshold levels, recovery from the poisoning occurs. Organochlorines are not cholinesterase inhibitors.

High tissue levels of some organochlorines (notably DDT, DDE, cyclodienes, mirex, and kepone) have been shown to induce hepatic microsomal drug-metabolizing enzymes. This tends to accelerate excretion of the pesticides themselves, but may also stimulate biotransformation of critical natural substances, such as steroid hormones and therapeutic drugs, occasionally necessitating reevaluation of required dosages in persons intensively exposed to organochlorines. Human absorption of organochlorine sufficient to cause enzyme induction is likely to occur only as a result of prolonged intensive exposure.

Hexachlorobenzene (a fungicide) has caused porphyria cutanea tarda in humans. It does not cause convulsions. Lindane, chlordane, and dieldrin have been associated anecdotally with certain rare hematologic disorders, including aplastic anemia; the incidence of these effects appears to be extremely low.

Poisoning by endosulfan has caused blindness in sheep. Mirex at high dosage produces cataracts in rats and mice. The DDT analogue known as DDD is selectively concentrated in adrenal tissue, where high levels have an inhibitory effect on corticosteroid synthesis, and a damaging effect on the cells. Certain other organochlorines are also bioconcentrated in the adrenal cortex.

SYMPTOMS AND SIGNS OF POISONING BY ORGANOCHLORINES

Early manifestations of poisoning by some organochlorine pesticides, particularly DDT, are often sensory disturbances: hyperesthesia and paresthesia of the face and extremities. Headache, dizziness, nausea, vomiting, incoordination, tremor, and mental confusion are also reported. More severe poisoning causes myoclonic jerking movements, then generalized tonic-clonic **CONVULSIONS**. The seizures may be followed by coma and respiratory depression.

Poisoning by the cyclodienes and toxaphene is more likely to begin with the sudden onset of convulsions, often not preceded by the premonitory manifestations mentioned above. Seizures caused by cyclodienes may appear as long as 48 hours after exposure, and may then recur periodically over several days following the initial episode. Because lindane and toxaphene are more rapidly biotransformed in the body and excreted, they are less likely than dieldrin, aldrin, and chlordane to cause delayed or recurrent seizures.

Poisoning by chlordecone has occurred as a result of extraordinary occupational exposure over many days. Principal manifestations were weight loss, tremor, muscle weakness, involuntary eye movements, pain in the chest and joints, skin rash, slurred speech, mental changes, and abnormalities of liver function. Seizures did not occur. Recovery was slow.

There have been no well documented reports of acute human poisonings by dicofol, mirex, heptachlor, dienochlor, perthane, methoxychlor, or chlorobenzilate.

CONFIRMATION OF POISONING BY ORGANOCHLORINES

Organochlorine pesticides and/or their metabolites can sometimes be identified in blood by gas-liquid chromotographic examination of samples taken within a few days of significant pesticide absorption. Such tests are performed by a limited number of government, university, and private laboratories, which can usually be contacted through poison control centers or health departments. Some organochlorine pesticides or their products (notably DDT, dieldrin, mirex, heptachlor epoxide, chlordecone) persist in tissues and blood for weeks or months after absorption, but others are likely to be excreted in a few days, limiting the likelihood of detection. Chromatographic methods make possible detection of most organochlorines at concentrations much lower than those associated with acute poisoning. Therefore, a positive finding in a tissue sample does not, of itself, justify a diagnosis of poisoning. To confirm poisoning, the measured concentration must be compared with those found in previously diagnosed cases of poisoning. DDT, DDE, and a few other organochlorines are still found at very low levels in blood samples from the general U.S. population, presumably due to past and/or current low level contamination of food by these environmentally persistent pesticides. There is presently no evidence that the small body burdens of organochlorines generated by foodborne residues cause disease in humans.

Samples of fat tissue are more likely to reveal stored organochlorines than blood. However, amounts of stored pesticides insufficient to be identified in blood are not likely to be of clinical significance. Measurements of urinary metabolites of some organochlorine pesticides can be useful in monitoring occupational exposures; however, the analytical methods are complex, and are not likely to detect amounts of metabolites generated by minimal exposures.

TREATMENT OF ORGANOCHLORINE TOXICOSIS

1. Persons exceptionally exposed to organochlorine pesticides by any route should be **OBSERVED** for sensory disturbances, incoordination, speech slurring, mental aberrations, and involuntary motor activity that would warn of imminent convulsions.
2. **IF CONVULSIONS OCCUR**, place the victim in the left lateral decubitus position with the head down. Move away furniture or other solid objects that may be a source of injury. If jaw movements are violent, place padded tongue blades between the teeth to protect the tongue. Whenever possible, remove dentures and other removable dental work. Aspirate oral and pharyngeal secretions, and, when possible, insert an oropharyngeal **AIRWAY** to maintain an open passage unobstructed by the tongue. Minimize noise and any manipulation of the patient that may trigger seizure activity.
3. Administer **OXYGEN** by mask. Maintain pulmonary gas exchange by mechanically assisted ventilation whenever respiration is depressed.
4. **CONTROL CONVULSIONS.** Drugs that are useful for this purpose are diazepam, lorazepam, barbiturates, and muscle-paralyzing agents such as succinylcholine.

   Benzodiazepine drugs are currently the preferred anticonvulsants.

   DIAZEPAM (Valium) has been tested the most extensively against convulsions and is generally recommended. **LORAZEPAM** (Ativan) may be superior as an anticonvulsant, but there is presently less clinical experience with its use for this purpose. It is possible that lorazepam or other drugs will prove to be superior in the future. Consult recent clinical toxicology texts for updated recommendations.

   Dosage of **DIAZEPAM:**

   Adults and children over 12 years: 5–10 mg given IV at no more than 2 mg per minute. Repeat every 10–15 minutes, if necessary, to a maximum of 30 mg.

   Children 5 to 12 years: 0.25–0.40 mg/kg body weight, slowly IV, and repeat every 10–15 minutes, if necessary, to a maximum of 10 mg.

   Children 30 days to 5 years: 0.25–0.40 mg/kg body weight, slowly IV, and repeat every 10–15 minutes, if necessary, to a maximum of 5 mg.

CAUTION: Administer slowly to avoid irritation of the vein, hypotension, and respiratory depression. Facilities should be immediately available to support pulmonary ventilation mechanically and to relieve laryngospasm.

If it is not possible to give the drug intravenously, administer the following doses undiluted by deep intramuscular injection:

Adults and children over 5 years: 10 mg. Repeat in 2-4 hours if necessary.

Children under 5 years: 5 mg. Repeat in 2-4 hours if necessary.

PENTOBARBITAL SODIUM is an intermediate acting barbiturate that is sometimes useful in controlling convulsions. It is supplied in stable injectable solution or may be prepared fresh as a 5% sterile aqueous solution (50 mg per ml). It can be given either intravenously or intramuscularly.

Dosage of **PENTOBARBITAL SODIUM:**

Adults and children over 12 years: 200-500 mg (4-10 ml). Initial intravenous dose should be 2-3 ml injected over a two-minute period. Wait five minutes to observe effect, then repeat if needed to suppress convulsions. If it is necessary to give pentobarbital intramuscularly, inject 2 ml deep at two different sites, then wait 20-30 minutes to observe effect. If needed, repeat intramuscular dose or switch to intravenous administration.

Children under 12 years: 3-7 mg/kg body weight injected over a five-minute period. Wait five minutes to observe effect, then repeat dose if necessary to suppress convulsions. If it is necessary to give intramuscularly, inject 1.5 mg/kg body weight at two different sites, then wait 20-30 minutes to observe effect. If necessary, repeat intramuscular dose or switch to intravenous administration.

CAUTION: Respiratory depression and hypotension may follow intravenous use of pentobartibal. Facilities must be immediately available to support pulmonary ventilation mechanically and to intubate the trachea if the upper airway is obstructed.

PHENYTOIN SODIUM (Dilantin) is effective in controlling epileptic seizures, but is of uncertain value against convulsions caused by chemical agents. Protocols for its administration can be found in medical texts dealing with the management of status epilepticus.

SUCCINYLCHOLINE (or similar muscle-paralyzing drug) may be used if seizures prove intractable. Gain full control of pulmonary ventilation (endotracheal tube or tracheostomy connected to a mechanical ventilator), prepare to monitor blood gases, and secure the services of an anesthesiologist or emergency care physician to induce general anesthesia and administer the neuromuscular depolarizing agent. This procedure predictably controls seizures, but imposes heavy responsibilities for continuous monitoring of gas exchange and blood pH over several hours.

5. In patients who have been poisoned by organochlorine contamination of skin, clothing, hair and/or eyes, **DECONTAMINATION MUST PROCEED CONCURRENTLY** with whatever resuscitative and anticonvulsive measures are necessary to preserve life. Contamination of the eyes should be removed by flushing with copious amounts of clean water. If the pesticide-exposed person remains alert and physically able, a prompt shower and shampoo may be appropriate, provided the patient is carefully observed to insure against sudden appearance of poisoning. If there are any indications of weakness, ataxia, or other neurologic impairment, clothing should be removed and a complete bath and shampoo given while the victim is recumbent, using copious amounts of soap and water. Attendants should wear rubber gloves. Surgical green soap is excellent for this purpose, but ordinary soap is about as good. The possibility of pesticide sequestered under fingernails or in skin folds should not be overlooked. **CONTAMINATED CLOTHING** should be promptly bagged and not returned until it has been thoroughly laundered. Contaminated leather shoes should be discarded. The possibility that pesticide has contaminated the inside surfaces of gloves, boots, and headgear should be considered.
6. **IF ORGANOCHLORINE HAS BEEN INGESTED** in a quantity sufficient to cause poisoning, the stomach and intestine must be emptied, and measures taken to limit toxicant absorption.

   Because seizure activity may develop rapidly, **LAVAGE,** with a large bore orogastric tube and with rigorous protection of the airway, is probably preferable to induced emesis in most cases. If the victim is convulsing, it is almost always necessary first to control seizures before attempting gastric intubation. The effectiveness of lavage in removing pesticide from the stomach diminishes rapidly with the passage of time. Procedures for emptying the stomach and administration of activated charcoal and cathartic are described in Chapter 1, TREATMENT, Section 6, p. 8.
7. Particularly in poisonings by large doses of organochlorine, **MONITOR PULMONARY VENTILATION** carefully to forestall respiratory failure. Assist pulmonary ventilation mechanically with oxygen whenever respiration is depressed.

8. In severely poisoned patients, **MONITOR CARDIAC STATUS** by continuous ECG recording to detect arrhythmias.
9. **DO NOT GIVE** epinephrine, other adrenergic amines, or atropine because of the enhanced myocardial irritability induced by chlorinated hydrocarbons, which predisposes to ventricular fibrillation.
10. **DO NOT GIVE** animal or vegetable oils or fats by mouth. They enhance gastrointestinal absorption of the lipophilic organochlorines.
11. To control seizures and myoclonic movements that sometimes persist for several days following acute poisoning by the more slowly excreted organochlorines, phenobarbital orally is likely to be effective. Dosage should be based on manifestations in the individual case and on information contained in the package insert.
12. **CHOLESTYRAMINE** resin accelerates the biliary-fecal excretion of the more slowly eliminated organochlorine compounds. It is usually administered in 4 gm doses, 4 times a day, before meals and at bedtime. Dose should be mixed with a pulpy fruit or liquid. Prolonged treatment (several weeks or months) may be necessary.
13. During convalescence, enhance **CARBOHYDRATE**, **PROTEIN**, and **VITAMIN** intake by diet or parenteral therapy.

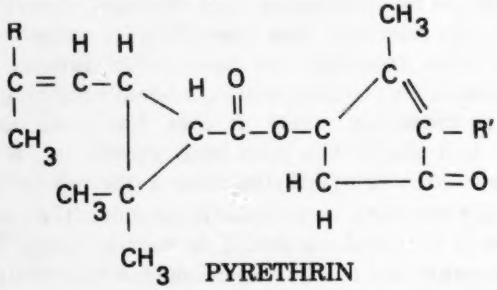
CHAPTER 4

INSECTICIDES OF BIOLOGICAL ORIGIN

This chapter concerns several widely used insecticidal products of natural origin, and also a growth promoting agent, gibberellic acid. It discusses, in order, pyrethrum and pyrethrins, nicotine, rotenone, sabadilla, bacillus thuringiensis, and gibberellic acid.

PYRETHRUM AND PYRETHRINS

GENERAL CHEMICAL STRUCTURE



PYRETHRIN

SOURCE AND PRODUCTS

Pyrethrum is the oleoresin extract of dried chrysanthemum flowers. The extract contains about 50% active insecticidal ingredients known as pyrethrins. The ketoalcoholic esters of chrysanthemic and pyrethroic acids are known as pyrethrins, cinerins, and jasmolins. These strongly lipophilic esters rapidly penetrate many insects and paralyze their nervous systems. Both crude pyrethrum extract and purified pyrethrins are contained in various commercial products, commonly dissolved in petroleum distillates. Some are packaged in pressurized containers ("bug-bombs"), usually in combination with the synergists piperonyl butoxide and n-octyl bicycloheptene dicarboximide. The synergists retard enzymatic degradation of pyrethrins. Some commercial products also contain organophosphate or carbamate insecticides. These are included because the rapid paralytic effect of pyrethrins on insects ("quick knockdown") is not always lethal.

Pyrethrum and pyrethrin products are used mainly for indoor pest control. They are not sufficiently stable in light and heat to remain as active residues on crops. The synthetic insecticides known as pyrethroids (chemically similar to pyrethrins) do have the stability needed for agricultural application. Pyrethroids are discussed in Chapter 5, p. 34.

TOXICOLOGY OF PYRETHRUM AND PYRETHRINS

Crude pyrethrum is a dermal and respiratory allergen, probably due mainly to noninsecticidal ingredients. Contact dermatitis and allergic respiratory reactions (rhinitis and asthma) have occurred following exposures. A strong cross-reactivity with ragweed pollen has been recognized. Single cases exhibiting anaphylactic and pneumonitic manifestations have also been reported. The refined pyrethrins are probably less allergenic, but appear to retain some irritant and/or sensitizing properties.

Pyrethrins are absorbed across the gut and pulmonary membrane, but only slightly across intact skin. They are very effectively hydrolyzed to inert products by mammalian liver enzymes. This rapid degradation combined with relatively poor bioavailability probably accounts in large part for their relatively low mammalian toxicity. Dogs fed extraordinary doses exhibit tremor, ataxia, labored breathing, and salivation. Similar neurotoxicity rarely, if ever, has been observed in humans, even in individuals who have used pyrethrins for body lice control (extensive contact) or pyrethrum as an anthelmintic (ingestion).

In cases of human exposure to commercial products, the possible role of other toxicants in the products should be kept in mind. The synergists piperonyl butoxide and n-octyl bicycloheptene dicarboximide have low toxic potential in humans, but organophosphates or carbamates included in the product may have significant toxicity. Pyrethrins themselves do not inhibit cholinesterase enzyme.

There are presently no practical tests for pyrethrin metabolites or pyrethrin effects on human enzymes or tissues that can be used to confirm absorption.

TREATMENT OF PYRETHRUM OR PYRETHRIN TOXICOSIS

Antihistamines are effective in controlling most allergic reactions. Severe asthmatic reactions, particularly in predisposed persons, may require administration of epinephrine, theophylline, and/or corticosteroid medicinals. Inhalation exposure should be carefully avoided in the future.

Contact dermatitis may require extended administration of topical corticosteroid preparations. This should be done under the supervision of a physician. Future contact with the allergen must be avoided.

Eye contamination should be removed by copious flushing of the eye with clean water or saline. Specialized care should be obtained if irritation persists.

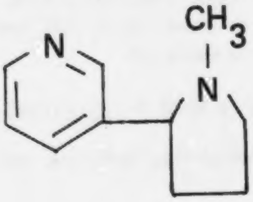
Toxic manifestations caused by other ingredients must be treated according to their respective toxic actions, independent of pyrethrin-related effects.

Even though most ingestions of pyrethrin products present little risk, if a large amount of pyrethrin-containing material has been ingested, it may be appropriate to empty the stomach by intubation, aspiration, and lavage, after all precautions have been taken to protect the respiratory tract from aspiration of stomach contents (see Chapter 1, TREATMENT, Section 6, p. 8). Lavage should be followed by instillation of activated charcoal and cathartic (see same reference).

If retained dosage was small and/or treatment has been delayed, and if patient is fully alert, **ORAL** administration of activated **CHARCOAL** and **CATHARTIC** probably represents optimal management. (See above reference for recommended dosages.)

NICOTINE

CHEMICAL STRUCTURE



SOURCE AND PRODUCTS

Nicotine is an alkaloid contained in the leaves of many species of plants, but is usually obtained commercially from tobacco. A 95% solution of the free alkaloid in organic solvent has been marketed in the past as a greenhouse fumigant. Another product used for the same purpose is a 40% aqueous solution of nicotine sulfate. Significant volatilization of nicotine occurs from both products. Commercial nicotine insecticides have long been known as Black Leaf 40. Formulations include sprays and dusts. Very little nicotine insecticide is used in the United States today; in fact, most nicotine poisonings are the result of ingestion of tobacco products.

TOXICOLOGY OF NICOTINE

Nicotine alkaloid is efficiently absorbed by the gut, lung, and skin. The sulfate salt is absorbed by lung and gut, but is poorly absorbed across the skin. Extensive biotransformation occurs in the liver resulting in a residence half-life of two hours or less. Both the liver and kidney participate in the formation and excretion of multiple end-products, which are excreted within a few hours.

Toxic action is complex, involving both stimulation and blockade of autonomic ganglia and skeletal muscle neuromuscular junctions, as well as direct effects on the central nervous system. Paralysis and vascular collapse are prominent features of acute poisoning, but death is usually due to respiratory paralysis, which may ensue promptly after the first symptoms of poisoning. Nicotine is not an inhibitor of cholinesterase enzyme.

MANIFESTATIONS OF NICOTINE POISONING

Early symptoms of poisoning are salivation, nausea, vomiting, and diarrhea. Burning sensations in the mouth and throat and abdominal pain are reported. If dosage has been high, vascular collapse, dyspnea then respiratory failure, cyanosis and unconsciousness may ensue promptly. Agitation, sweating, headache, pupillary constriction, dizziness, incoordination, confusion, weakness, tremor, and convulsions occur early in less fulminant poisoning. Initial hypertension is probably due mainly to generalized vasoconstriction. Subsequent shock is caused by vasodilatation, often associated with vagotonic asystole or severe cardiac arrhythmias. Respiratory failure is caused mainly by paralysis of the muscles of respiration.

CONFIRMATION OF NICOTINE POISONING

Urine content of the metabolite cotinine can be used to confirm absorption of nicotine.

TREATMENT OF NICOTINE TOXICOSIS

1. If liquid or aerosol spray has come in contact with skin, wash the area thoroughly with soap and water.
2. If eyes have been contaminated, flush them thoroughly with clean water or saline. If irritation persists, obtain specialized medical treatment.
3. If symptoms of poisoning appear during exposure to an airborne nicotine insecticide, remove the person from the contaminated environment immediately, wash any skin areas that may be contaminated, then transport the victim to the nearest treatment facility. Although mild poisoning may resolve without treatment, it is often difficult to predict the ultimate severity of poisoning at the onset.
4. If there is any indication of loss of respiratory drive, **MAINTAIN PULMONARY VENTILATION** by mechanical means, including supplemental **OXYGEN**, if available, by mouth-to-mouth, or mouth-to-nose methods, if necessary. Toxic effects of nicotine other than respiratory depression are usually survivable. The im-

portance of maintaining adequate gas exchange is therefore paramount.

5. If a nicotine-containing product has been ingested, immediate steps must be taken to limit gastrointestinal absorption.
   - A. **IF** the patient is fully **ALERT,** immediate oral administration of **ACTIVATED CHARCOAL** is probably the best initial step in management.

     Dosage of **ACTIVATED CHARCOAL:**

     Adults and children over 12 years: 50–100 gm in 300–800 ml water.

     Children under 12 years: 15–30 gm in 100–300 ml water.

     Because nicotine itself is very likely to induce diarrhea, it is usually not appropriate to include cathartic with the charcoal.

     CAUTION: Because unconsciousness may develop rapidly in nicotine poisoning, it is essential to position the patient after the charcoal slurry has been swallowed (recumbent prone, head down) so that vomited material will not be aspirated.
   - B. If the patient is unconscious or confused, the stomach should be emptied by **INTUBATION, ASPIRATION,** and **LAVAGE,** after all precautions have been taken to protect the respiratory tract from aspirated stomach contents (see Chapter 1, TREATMENT, Section 6, p. 8). Charcoal slurry should be used in washing the stomach, and several ounces should be left in the stomach after the lavage. Repeated administration of activated charcoal at half or more the initial dosage every 2–4 hours may be beneficial.
   - C. **DO NOT** administer Syrup of Ipecac. It may enhance medullary depressant effects of nicotine, and may induce vomiting when the patient is obtunded.

6. Monitor cardiac status by electrocardiography, and measure blood pressure frequently. Cardiopulmonary resuscitation may sometimes be necessary.

   Vascular collapse may require administration of norepinephrine and/or dopamine. Consult package inserts for dosages and routes of administration. Infusions of electrolyte solutions, plasma and/or blood may also be required to combat shock.

7. There is no specific antidote for nicotine poisoning. Severe hypersecretion (especially salivation and diarrhea) may be controlled by intravenous atropine sulfate.

   Dosage of **ATROPINE SULFATE:**

   Adults and children over 12 years: 0.4–0.5 mg slowly IV, repeated every 5 minutes if necessary.

   Children under 12 years: 0.01 mg/kg body weight, slowly IV, repeated every 5 minutes if necessary.

CAUTION: Careful ECG monitoring of cardiac rhythm should accompany intravenous administration of atropine.

8. Convulsions should be controlled with diazepam or other benzodiazepine drug. See Chapter 3, TREATMENT, Section 4 (p. 21) for appropriate dosages and methods of administration.
9. If the patient survives for four hours, complete recovery is said to be likely.

ROTENONE

SOURCE AND PRODUCTS

Although this natural substance is present in a number of plants, the source of most rotenone used in the United States is the dried derris root imported from Central and South America. It is formulated as dusts, powders, and sprays (less than 5% active ingredient) for use in gardens and on food crops. Many products contain piperonyl butoxide as synergist, and other pesticides are included in some commercial products. Rotenone degrades rapidly in the environment. Emulsions of rotenone are applied to lakes and ponds to kill fish.

COMMERCIAL PRODUCTS

Noxfish, Noxfire, Rotacide, Foliafume, Nusyn-Noxfish, PB-Nox, Prentox, Chem-Fish, Rotenone Solution FK-11.

TOXICOLOGY AND MANIFESTATIONS OF POISONING

Although rotenone is toxic to the nervous systems of insects, fish, and birds, commercial rotenone products have presented little hazard to man over many decades. Neither fatalities nor systemic poisonings in humans have been reported in relation to ordinary use. Low concentration in commercial products, degradability, an intense nauseant effect in man, and poor absorption across gut and skin are probable factors accounting for the good safety record of rotenone.

Numbness of oral mucous membranes has been reported in workers who got dust from the powdered derris root in their mouths. Dermatitis and respiratory tract irritation have also been reported in occupationally exposed persons.

When rotenone has been injected into animals, tremors, vomiting, incoordination, convulsions, and respiratory arrest have been observed. These effects have not been reported in occupationally exposed humans.

TREATMENT OF ROTENONE TOXICOSIS

Skin contamination should be removed by washing with soap and water. Eye contamination should be removed by flushing the eye thoroughly with clean water or saline. Dust in the mouth should be washed out. If irritation persists, medical treatment should be obtained.

If a rotenone-containing product has been swallowed and retained, active efforts to empty the stomach should be undertaken only if another more toxic pesticide is contained in the product. If patient is fully alert, prompt oral administration of activated charcoal (and cathartic if diarrhea has not already occurred) is probably the optimal management of ingestion of a product containing rotenone as the only insecticidal ingredient (with or without synergists). See Chapter 1, TREATMENT, Section 6, p. 8 for dosages.

SABADILLA

SOURCE AND PRODUCTS

Sabadilla consists of the powdered ripe seeds of a South American lily. It is used as a dust, with lime or sulfur, or dissolved in kerosene, mainly to kill ectoparasites on domestic animals and humans. Insecticidal alkaloids are those of the veratrin type. The concentration of alkaloids in commercial sabadilla is usually less than 0.5%. Little or no sabadilla is used in the United States today, but there is probably some used in other countries.

TOXICOLOGY OF SABADILLA

Sabadilla dust is very irritating to the upper respiratory tract, causing sneezing, and is also irritating to the skin.

Veratrin alkaloids are apparently absorbed across the skin and gut, and probably by the lung as well. Veratrin alkaloids have a digitalis-like action on the heart muscle (impaired conduction and arrhythmias).

MANIFESTATIONS OF SABADILLA POISONING

Although poisoning by medicinal veratrin preparations may have occurred in the remote past, systemic poisoning by sabadilla preparations used as insecticides has been very rare or nonexistent.

TREATMENT OF SABADILLA TOXICOSIS

Contaminated skin should be washed thoroughly with soap and water. If eyes are affected, they should be flushed with copious amounts of clean water or saline. If skin or eye irritation persists, medical treatment should be obtained.

If a large amount of sabadilla pesticide product has been ingested in the past hour and retained, the stomach should be emptied by intubation, aspiration, and lavage (see Chapter 1, TREATMENT, Section 6). If only a small amount of sabadilla pesticide has been ingested and retained, or if treatment is delayed, and if the patient remains fully alert, immediate oral administration of activated charcoal probably represents optimal management. If diarrhea has not already commenced, sorbitol should be administered with the charcoal slurry (see above reference). If there is a suspicion that significant amounts of sabadilla alkaloids have been absorbed, ECG monitoring of cardiac activity for arrhythmias and conduction defects is appropriate.

BACILLUS THURINGIENSIS

SOURCE AND PRODUCTS

Several strains of the Bacillus thuringiensis are pathogenic to some insects. The bacterial organisms are cultured, then harvested in spore form for use as insecticide. Production methods vary widely. Proteinaceous and nucleotide-like toxins generated by the vegetative forms (which infect insects) are responsible for the insecticidal effect. The spores are formulated as wettable powders, flowable concentrates and granules for application to field crops and for control of mosquitoes and black flies.

COMMERCIAL PRODUCTS

Variety kurstaki: Bactur, Bactospeine, Dipel, Futura, Sok-Bt, Thuricide, Tribactur. Variety israelensis: Bactimos, Skeetal, Teknar, Vectobac. Variety aizawai: Certan.

TOXICOLOGY OF BACILLUS THURINGIENSIS

The varieties of Bacillus thuringiensis used commercially survive when injected into mice, and at least one of the purified insecticidal toxins is toxic to mice. Infections of humans have been extremely rare (two recognized cases) and no occurrences of human toxicosis have been reported. From studies involving deliberate ingestion by human subjects, it appears possible, but not likely, that the organism can cause gastroenteritis. B. thuringiensis products are exempt from tolerance on raw agricultural commodities in the United States. Neither irritative nor sensitizing effects have been reported in workers preparing and applying commercial products.

TREATMENT OF BACILLUS THURINGIENSIS TOXICOSIS

Skin contamination should be removed with soap and water. Eye contamination should be removed by flushing the eyes with clean water or saline. If irritation persists, or if there is any indication of infection, treatment by a physician should be obtained.

If a B. thuringiensis product has been ingested, the patient should be observed for manifestations of bacterial gastroenteritis: abdominal cramps, vomiting, and diarrhea. The illness is likely to be self-limited if it occurs at all. Kaolin- and pectin-containing medicinals may mitigate the symptoms. If dehydration is marked, saline- and glucose-containing fluids may be given orally or intravenously. Buttermilk may be given to restore normal gut flora.

A single case of corneal ulcer caused by a splash of B. thuringiensis suspension into the eye was successfully treated by subconjunctival injection of gentamicin (20 mg) and cephazolin (25 mg).

GIBBERELLIC ACID (Gibberellin, GA_3)

SOURCE AND PRODUCTS

Gibberellic acid is not a pesticide, but it is commonly used in agricultural production as a growth promoting agent. It is a metabolic product of a cultured fungus, formulated in tablets, granules, and liquid concentrates for application to soil beneath growing plants and trees.

Commercial products: Activol, Berelex, Cekugib, Gibberellin, Gibrel, Grocel, Pro-Gibb, Pro-Gibb Plus, Regulex.

TOXICOLOGY OF GIBBERELLIC ACID

Experimental animals tolerate large oral doses without apparent adverse effect. No human poisonings have been reported. Sensitization has not been reported, and irritant effects are not remarkable.

MANAGEMENT OF GIBBERELLIC ACID EXPOSURE

Wash contamination from skin with soap and water. Flush contamination from eyes with clean water or saline. If irritation occurs, obtain medical treatment.

If gibberellic acid has been swallowed, there is no reason to expect adverse effects.

Chapter 5

OTHER INSECTICIDES, ACARICIDES, AND REPELLENTS

This chapter concerns insecticides, acaricides, and repellents having toxicologic characteristics distinct from the insecticides discussed in previous chapters. It discusses pyrethroids, fluorides, borates, chlordimeform, propargite, substituted haloaromatic urea compounds, chlorobenzilate, cyhexatin, methoprene, sulfur, diethyltoluamide, alkyl phthalates, and benzyl benzoate.

PYRETHROIDS

These modern synthetic insecticides are similar chemically to natural pyrethrins, but modified to increase stability in the natural environment. They are now widely used in agriculture, in homes and gardens, and for treatment of ectoparasitic disease.

COMMERCIAL PRODUCTS

The following list includes the names of several pyrethroids that are not currently in commercial production. These are included because they may be marketed in the future, if not in the United States, then possibly in other countries.

Allethrin (Pynamin), alphametrin, barthrin, bioresmethrin, biopermethrin, cismethrin, cyclethrin, cyfluthrin (Baythroid), cypermethrin (Ammo, Barricade, CCN52, Cymbush, Cymperator, Cyperkill, Folcord, KafilSuper, NRDC 149, Polytrin, Siperin, Ripcord, Flectron, Ustaad, Cyrux), deltamethrin (decamethrin, Decis), dimethrin, fenpropathrin (Danitol, Herald, Meothrin, Ortho Danitol, Rody), fenvalerate (Pydrin, Belmark, Sumicidin, Fenkill), flucythrinate (AASTAR, Pay-off), fluvalinate (Mavrik, Mavrik Aquaflow, Spur), furethrin, indothrin, permethrin (Ambush, BW-21-Z, Ectiban, Eksmin, Kafil, Permasect, Perthrine, Pounce, Pramex, Outflank, Talcord), phthalthrin (Neopynamin), resmethrin (Benzofuroline, Chrysron, Pynosect, Synthrin), tetramethrin (Neopynamin, Phthalthrin), tralomethrin (Scout), esfenvalerate (Asana).

Pyrethroids are formulated as emulsifiable concentrates, wettable powders, granules, and concentrates for ultra low volume application. They may be combined with additional pesticides (sometimes highly toxic) in the technical product or tank mixed with other pesticides at the time of application. AASTAR is a combination of flucythrinate and phorate. Phorate is a highly toxic organophosphate.

Nix is a 1% permethrin creme applied to control human ectoparasites.

TOXICOLOGY OF PYRETHROIDS

Although certain pyrethroids exhibit striking neurotoxicity in laboratory animals when administered by intravenous injection, and some are toxic by the oral route, systemic toxicity by inhalation and dermal absorption is low. There have been very few systemic poisonings of humans by pyrethroids. Although limited absorption may account for the low toxicity of some pyrethroids, rapid biodegradation by mammalian liver enzymes (ester hydrolysis and oxidation) is probably the major factor responsible. Most pyrethroid metabolites are promptly excreted, at least in part, by the kidney.

Extraordinary absorbed doses may rarely cause incoordination, tremor, salivation, vomiting, diarrhea, and irritability to sound and touch. Extreme doses have caused convulsions in laboratory animals.

Apart from systemic neurotoxicity, some pyrethroids do cause distressing paresthesia when liquid or volatilized materials contact human skin. Sensations are described as stinging, burning, itching, and tingling, progressing to numbness. The skin of the face seems to be most commonly affected, but the hands, forearms, and neck are sometimes involved. Sweating, exposure to sun or heat, and application of water enhance the disagreeable sensations. Sometimes the effect is noted within minutes of exposure, but a 1-2 hour delay in appearance of symptoms is more common. Sensations rarely persist more than 24 hours. Little or no inflammatory reaction is apparent where the paresthesia are reported; the effect is presumed to result from pyrethroid contact with sensory nerve endings in the skin. Not all pyrethroids cause a marked paresthetic reaction: it is prominent following exposure to pyrethroids whose structures include cyano-groups: fenvalerate, flucythrinate, cypermethrin, and fluvalinate. The paresthetic reaction is not allergic in nature: sensitization does not occur. Neither race, skin type, nor disposition to allergic disease affect the likelihood or severity of the reaction.

Persons treated with permethrin for lice or flea infestations sometimes experience itching and burning at the site of application, but this is chiefly an exacerbation of sensations caused by the parasites themselves, and is not typical of the paresthetic reaction described above.

The manifestations of neurologic disorder seen in laboratory animals given the more toxic pyrethroids in large doses are salivation, irritability, tremors, ataxia, choreoathetosis (writhing convulsions), fall in blood pressure, and death. Severe metabolic acidosis is characteristic.

Due to the inclusion of unique solvent ingredients, certain formulations of fluvalinate are corrosive to the eyes (see TREATMENT, Section 2, this chapter).

Pyrethroids are not cholinesterase inhibitors.

TREATMENT OF PYRETHROID TOXICOSIS

1. Skin contamination should be removed promptly by washing with soap and water. If irritant or paresthetic effects occur, treatment by a physician should be obtained. Because volatilization of pyrethroid apparently accounts for paresthesia affecting the face, strenuous measures should be taken (ventilation, protective face mask and hood) to avoid vapor contact with the face and eyes. Vitamin E Oil preparations (dl-alpha tocopheryl acetate) are uniquely effective in preventing and stopping the paresthetic reaction. They are safe for application to the skin under field conditions. Corn oil is somewhat effective, but possible side effects with continuing use make it less suitable. Vaseline is less effective than corn oil and zinc oxide actually worsens the reaction.
2. Eye contamination should be treated immediately by prolonged flushing of the eye with copious amounts of clean water or saline. If irritation persists, professional ophthalmologic care should be obtained. Undiluted Mavrik 2E (a formulation of fluvalinate) is corrosive to the eyes. Extraordinary measures should be taken to avoid eye and skin contamination with this product. Should accidental eye contamination occur, expert ophthalmologic care should be obtained after flushing the eye free of the chemical with copious amounts of clean water.
3. Ingestion of pyrethroid insecticide presents relatively little risk. However, if large amounts have been ingested, empty the stomach by **INTUBATION, ASPIRATION,** and **LAVAGE** (see Chapter 1, TREATMENT, Section 6, p. 8). Based on observations in laboratory animals, large ingestions of either allethrin, cismethrin, fenvalerate or deltamethrin would be the most likely to generate neurotoxic manifestations.
4. If only small amounts of pyrethroid have been ingested, or if treatment has been delayed, oral administration of activated charcoal and cathartic probably represents optimal management (see Chapter 1, TREATMENT, Section 6, p. 8 for dosages).
5. Several drugs are effective in relieving the pyrethroid neurotoxic manifestations observed in deliberately poisoned laboratory animals. None have been tested in human poisonings; therefore, neither efficacy nor safety under these circumstances is known. Furthermore, moderate neurotoxic symptoms and signs are likely to resolve spontaneously if they do occur. Drugs effective in laboratory animals that might be considered for symptomatic treatment are: atropine (relief of salivation), diazepam, and phenobarbital (relief of tremors and convulsions), and mephenesin (relief of all poisoning manifestations, except, sometimes, salivation).

FLUORIDES

COMMERCIAL PRODUCTS

Sodium fluoride is a crystalline mineral once widely used in the United States for control of larvae and crawling insects in homes, barns, warehouses and other storage areas. It is highly toxic to all plant and animal life.

Commercial product: Florocid

Sodium fluosilicate (sodium silico fluoride) has been used to control ectoparasites on livestock, as well as crawling insects in homes and work buildings. It is approximately as toxic as sodium fluoride.

Commercial products: Safsan (dust formulation)
Prodan (bait formulation)

Sodium fluoaluminate (sodium aluminofluoride, cryolite) is a stable mineral containing fluoride. It is used as an insecticide on some vegetables and fruits. Cryolite has very low water solubility, does not yield fluoride ion on decomposition, and presents very little toxic hazard to mammals, including man.

Commercial product: Kryocide

Hydrofluoric acid is an important industrial toxicant, but is not used as a pesticide. Fluoroacetate is discussed in Chapter 13: RODENTICIDES. Sulfuryl fluoride is discussed in Chapter 14: FUMIGANTS.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY FLUORIDE

Sodium fluoride and fluosilicate used as insecticides present a serious toxic hazard to humans because of high inherent toxicity, and the possibility that children crawling on floors of treated dwellings will ingest the material.

Absorption across the skin is probably slight, and methods of pesticide use rarely include a hazard of inhalation, but uptake of ingested fluoride by the gut is efficient and potentially lethal. Excretion is chiefly in the urine: renal clearance of fluoride from the blood is rapid. However, large loads of absorbed fluoride poison renal tubule cells. Functional tubular disturbances and sometimes acute renal failure result.

The toxic effects of fluoride in mammals are multiple and all may threaten life. Except for the direct effect on ionized calcium in extracellular fluid, the actions of fluoride result from inhibition of critical intracellular enzymes.

Ingested fluoride has a corrosive effect on the epithelial lining of the gastrointestinal tract, due, in part, to highly corrosive hydrofluoric acid formed in the stomach. Edema, ulceration, and hemorrhage commonly result. Thirst, abdominal pain, vomiting, and diarrhea, with blood in vomitus and feces usually occur.

Absorbed fluoride ion reduces extracellular fluid concentrations of calcium and magnesium. Hypocalcemia sometimes results in tetany. Hyperkalemia is sometimes a serious threat to the heart.

Cardiac arrhythmias and shock are often prominent features of poisoning. These probably result from combinations of effects of fluid and electrolyte disturbances and direct actions of fluoride on heart and vascular tissues. Hypotension and severe arrhythmias, sometimes progressing to ventricular fibrillation, characterize severe poisonings.

Toxic actions on the brain are manifest as headache, muscular weakness, salivation, nystagmus, dilated pupils, lethargy, stupor and coma.

Occasionally, convulsions occur. Respiratory failure is usually the immediate cause of death.

CONFIRMATION OF POISONING

Plasma inorganic fluoride concentrations in the general United States population are usually less than 0.02 milligram per liter and rarely above 0.10 milligram per liter. In fatal cases of poisoning, plasma levels from 3.5 to 15.5 milligrams per liter have been recorded.

TREATMENT OF FLUORIDE TOXICOSIS

1. Contamination of the skin should be removed by washing with soap and water. Eye contamination should be removed by prolonged flushing of the eye with copious amounts of clean water or saline. If irritation persists, specialized medical treatment should be obtained.
2. If **SODIUM FLUORIDE OR SODIUM FLUOSILICATE** has been **INGESTED**, immediate steps must be taken to remove or neutralize the toxicant.
    - A. If the victim is fully alert, and if vomiting does not totally prevent swallowing of a neutralizing agent, prompt oral administration of lime water (0.15% calcium hydroxide), 1% calcium chloride solution, calcium- or magnesium-based antacid or aluminum hydroxide gel (antacid gel preparation), or milk will precipitate the bulk of fluoride ion in the gut and therefore may be lifesaving. The victim should be given as much as can be tolerated.
    - B. If the victim is obtunded or if vomiting precludes oral administration, the airway should be protected by endotracheal intubation, then the stomach should be gently intubated and lavaged with several ounces of one of the liquids named in 2A.

above. Activated charcoal does not bind fluoride ion and is therefore of no value in fluoride poisoning.

3. A blood specimen should be drawn for blood electrolyte analysis: sodium, potassium, calcium, magnesium, fluoride, and bicarbonate capacity. Another sample should be drawn to type and crossmatch for blood transfusion. Intravenous fluids (initially 5% dextrose in 0.9% saline) should be started to combat dehydration, shock and metabolic acidosis. Fluid balance should be monitored closely to forestall fluid overload if renal failure occurs. If metabolic acidosis is detected, sodium bicarbonate should be administered to keep the urine at pH 7.0–7.5. Intravenous fluids must be stopped if anuria or oliguria (less than 25–30 ml per hour) develops. If urine formation declines, extracorporeal hemodialysis should be used. It removes fluoride efficiently, but no more rapidly than a normally functioning kidney.
4. Monitor cardiac status by continuous electrocardiography. Ventricular arrhythmias may necessitate DC cardioversion.
5. If overt or latent (Chvostek's sign) tetany occurs, or if hypocalcemia is demonstrated, or if it appears likely that a significant amount of fluoride has been absorbed, administer 10 ml of 10% **calcium gluconate** intravenously, at no more than one ml per minute. Initial children's dose is approximately 0.5 ml/kg body weight. Repeat in 10–20 minutes if there are still indications of hypocalcemia. Severe poisonings may require administration of several hundred milliliters of 10% calcium gluconate.
6. **OXYGEN** by mask should be administered for hypotension, shock, cardiac arrhythmias, or cyanosis. Shock may require administration of plasma or blood.

SODIUM FLUOALUMINATE (CRYOLITE) is much less toxic than other fluorides. If a very large amount has been ingested, it may be appropriate to measure serum calcium to insure that hypocalcemia has not occurred. If so, intravenous 10% calcium gluconate would be indicated (see 5 above). It is unlikely that treatment for fluoride toxicity would be necessary following ingestion of sodium fluoaluminate.

BORIC ACID AND BORATES

COMMERCIAL PRODUCTS

Boric acid, sodium tetraborate decahydrate (borax), sodium pentaborate, boron trioxide, sodium biborate.

Commercial products: Polybor, Pyrobor

Formulated as tablets and powder to kill larvae in livestock confinement areas and cockroaches in residences. Rarely, solutions are sprayed as a nonselective herbicide.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY BORATE

Borax dust is moderately irritating to skin. Inhaled dust causes irritation of the respiratory tract: cough and shortness of breath.

There have been few poisonings from the pesticidal uses of borates, although powders and pellets scattered on the floors of homes do present a hazard to children. Most poisonings have resulted from injudicious uses in human medicine aimed at suppressing bacterial growth, such as compresses for burns. Many poisonings of newborns occurred in the 1950's and 1960's.

Borates are well absorbed by the gut and by abraded or burned skin, but not by intact skin. They are efficiently excreted by the kidney. The residence half-life in humans averages 13 hours, in a range of 4-28 hours.

The gastrointestinal tract, skin, vascular system, and brain are the principal organs and tissues affected. Nausea, persistent vomiting, abdominal pain, and diarrhea reflect a toxic gastroenteritis, which occurs even when the borate was absorbed across damaged skin. Blood in vomitus and feces reflect hemorrhagic lesions in the gut mucosa. In severe poisonings of infants, a beefy red skin rash, most often affecting palms, soles, buttocks, and scrotum, has been described. It has been characterized as a "boiled lobster appearance." The intense erythema is followed by extensive exfoliation.

Cyanosis, weak pulse, and cold clammy skin indicate shock, which is sometimes the cause of death in borate poisoning.

Headache, weakness, lethargy, restlessness, and tremors may progress to intermittent seizures. Unconsciousness and respiratory depression signify life-threatening brain injury.

Acute renal failure (oliguria or anuria) may be a consequence of shock, of direct toxic action on renal tubule cells, or both. It occurs only in severe borate poisoning. Metabolic acidosis may be a consequence of the acid itself, of seizure activity, or of metabolic derangements. Fever is sometimes present in the absence of infection.

A recent analysis of 784 cases of **ACUTE SINGLE-DOSE BORATE INGESTION** (excluding newborns and cases of protracted exposure) has indicated a much more favorable prognosis than that which was based on neonate poisonings in the 1950's and 1960's (50%-70% mortality). In the recent survey (Litovitz, T. L. et al. Am. J. Emergency Med. 6(3):209-213, 1988), only 12% of cases were even symptomatic, and there were no fatalities. In those who became symptomatic, gastrointestinal symptoms (vomiting, abdominal pain, diarrhea) predominated.

Central nervous system manifestations and rash were rare and of brief duration when they did occur.

CONFIRMATION OF POISONING

Borate can be measured in serum by a colorimetric procedure, using carminic acid as a chromogen. Blood borate concentrations in non-exposed individuals are in the range of 0.0–7.2 mg per liter (average 1.4 mg per liter). Excluding newborns and chronically exposed individuals, serum borate concentrations less than 340 mg per liter have rarely been associated with significant toxicity.

A paper spot test for borate in the urine may be helpful in identifying urine borate concentrations greater than 20 mg per liter. Urine acidified with hydrochloric acid and applied to turmeric paper produces a brownish-red color if borate is present. A recent evaluation has warned, however, that a significant number of false positives may be encountered when this test is used.

TREATMENT OF BORATE TOXICOSIS

1. Dermal contamination should be removed by washing with soap and water. Contamination of the eye should be treated by prolonged flushing with copious amounts of saline or water. If irritation persists, specialized medical treatment should be obtained.
2. The great majority of *pesticidal* borate poisonings are likely to be acute (single dose) ingestions and are unlikely to occur in newborns. A recently recommended protocol for management of acute borate ingestion (excluding newborns and chronically exposed persons) is as follows (from above reference):

Patient's Weight, kg	*Dose of Borate*	*Recommended Management*
Less than 30 kg	Less than 200 mg/kg	Observation only
	200–400 mg/kg	Syrup of Ipecac
	Greater than 400 mg/kg	Syrup of ipecac or gastric lavage
Greater than 30 kg	Less than 6.0 gm	Observation only
	6.0–12.0 gm	Syrup of Ipecac
	Greater than 12.0 gm	Syrup of Ipecac or gastric lavage

Dosage of Syrup of Ipecac for adults and children over 12 years is 30 ml; dosage for children under 12 years is 15 ml. Follow Syrup of Ipecac with 2–3 glasses of water. Watch closely for declining consciousness level; insure that victim is in a head down left lateral decubitus position when vomiting occurs. Protocol for gastric lavage is set forth in Chapter 1, TREATMENT, Section 6, page 8. Activated charcoal does not adsorb borate and therefore should not be given unless an additional toxicant was ingested which is charcoal-adsorbable.

Obtain a blood sample 2-3 hours post-ingestion to assess severity of poisoning, but do not base initial therapy on blood concentration.

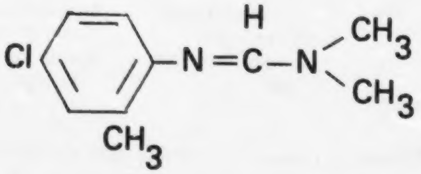
3. **IF INGESTION** of borate has been **MASSIVE** (several grams), or has extended over several days, administer intravenous glucose and electrolyte solutions to sustain urinary excretion of borate. Monitor fluid balance and blood electrolytes (including bicarbonate capacity) regularly. Monitor cardiac status by ECG. Test the urine for protein and cells to detect renal injury, and monitor serum concentration of borate. If metabolic acidosis is detected, sodium bicarbonate should be added to the infused fluids to keep urine pH in the 7.0-7.5 range. If shock develops, it may be necessary to infuse plasma or whole blood. Administer oxygen continuously. If oliguria (less than 25-30 ml urine formed per hour) occurs, intravenous fluids must be slowed or stopped to avoid overloading the circulation.

   A. Both peritoneal dialysis and extracorporeal hemodialysis have been used with apparent success in accelerating elimination of borate. If renal failure occurs, hemodialysis may be necessary to sustain fluid balance and normal extracellular fluid composition. In poisoned infants, exchange blood transfusion has been used successfully.

   B. Control convulsions with benzodiazepine drugs or other anticonvulsants, if necessary (see Chapter 3, TREATMENT, Section 4, page 21).

CHLORDIMEFORM

STRUCTURE



COMMERCIAL PRODUCTS

Bermat, Fundal, Galecron, Ovatoxin.

Formulations are emulsifiable concentrates and water-soluble powders. Chlordimeform is an ovicide and acaricide.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY CHLORDIMEFORM

In a reported episode of occupational exposure to chlordimeform, several workers developed hematuria. Hemorrhagic cystitis, probably due to chloraniline biodegradation products, was the source of the blood in the urine. Symptoms reported by the affected workers were: gross blood in the urine, painful urination, urinary frequency and urgency, penile discharge, abdominal and back pain, a generalized "hot" sensation, sleepiness, skin rash and desquamation, a sweet taste, and anorexia. Symptoms persisted for 2-8 weeks after exposure was terminated.

Chlordimeform is not a cholinesterase inhibitor. Although methods do exist for measurement of urinary excretion products, these tests are not generally available.

TREATMENT OF CHLORDIMEFORM TOXICOSIS

Strenuous efforts should be made to protect against inhalation and dermal contact with chlordimeform because absorption is evidently efficient. Skin contamination should be washed off with soap and water. Contamination of the eye should be treated by flushing with copious amounts of clean water or saline. If irritation persists, specialized medical treatment should be obtained.

If chlordimeform has been ingested no more than several hours prior to treatment, and if the patient is fully alert, administer Syrup of Ipecac, followed by several glasses of water, to empty the stomach. Dosage for adults and children over 12 years: 30 ml; dosage for children under 12 years: 15 ml.

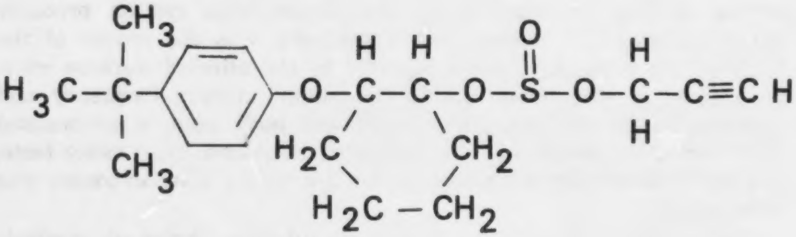
If the patient is obtunded, the operation of a different or additional toxicant should be suspected. In this event, the stomach should be emptied by intubation, aspiration and lavage with a slurry of activated charcoal in water or saline, after measures have been taken to protect the respiratory tract from aspiration of gastric contents (see Chapter 1, TREATMENT, Section 6, p. 8).

After the stomach has been emptied, activated charcoal and a cathartic should be administered (see above reference). Repeated doses of charcoal every 2-4 hours may be beneficial. Because catharsis may cause serious dehydration and electrolyte disturbances in young children, fluid balance and serum electrolytes should be monitored. An adequate state of hydration should be maintained by oral and/or intravenous fluids to support chlordimeform excretion.

Repeated analyses of urine for protein and red cells should be done to detect injury to the urinary tract. Disappearance of hematuria can ordinarily be expected in 2-8 weeks. Relief from other symptoms can usually be expected earlier.

PROPARGITE

STRUCTURE



COMMERCIAL PRODUCTS

Omite, Comite, Uniroyal D014.

Formulations are wettable powders and emulsifiable concentrates. Propargite is an acaricide with residual action.

TOXICOLOGY AND ADVERSE EFFECTS OF PROPARGITE

Propargite exhibits very little systemic toxicity in animals. No systemic poisonings have been reported in humans. However, many workers having dermal contact with this acaricide have experienced skin irritation and possibly sensitization in some cases. Eye irritation has also occurred. For this reason, stringent measures should be taken to prevent inhalation or any skin or eye contamination by propargite.

There is no readily available method for detecting absorption of propargite.

TREATMENT OF PROPARGITE TOXICOSIS

Skin contamination should be removed by prompt washing with soap and water. Eye contamination should be treated by flushing with copious amounts of clean water or saline. If irritation persists, specialized medical treatment should be obtained. Sensitization reactions may require steroid therapy.

If large amounts of propargite have been ingested, and effective vomiting has not occurred, and if there are no indications of nervous system depression, administration of Syrup of Ipecac, followed by several glasses of water, is probably the appropriate method to empty the stomach. Dosage for adults and children over 12 years: 30 ml; dosage for children under 12 years: 15 ml.

If there are indications of central nervous system depression, empty the stomach by intubation, aspiration, and lavage with a slurry of activated charcoal, having first taken precautions to prevent aspiration of stomach contents (see Chapter 1, TREATMENT, Section 6, p. 8). Follow the lavage with instillation of activated charcoal (see above reference). Include sorbitol in the charcoal instillation if diarrhea has not already commenced.

If the amount of propargite ingested was small, or if treatment is delayed, oral administration of activated charcoal and sorbitol probably represents optimal management.

DIFLUBENZURON

COMMERCIAL PRODUCTS

Dimilin, Micromite.

This is a haloaromatic substituted urea which controls insects by impairing chitin deposition in the larval exoskeleton. It is formulated in wettable powders, oil dispersible concentrate, and granules for use in agriculture and forestry and in settings where fly populations tend to be large, such as feedlots.

TOXICOLOGY OF DIFLUBENZURON

There is limited absorption across the skin and intestinal lining of mammals, after which enzymatic hydrolysis and excretion rapidly eliminate the pesticide from tissues. Irritant effects are not reported and systemic toxicity is low. Methemoglobinemia is a theoretical risk from chloroaniline formed hydrolytically, but no reports of this form of toxicity have been reported in humans or animals from diflubenzuron exposure.

Treatment of contamination and ingestions should proceed essentially as outlined in the previous section (Propargite).

TEFLUBENZURON

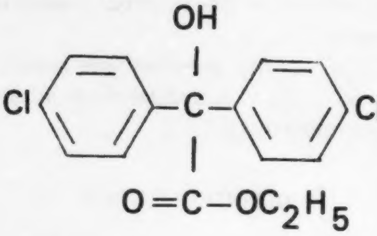
COMMERCIAL PRODUCTS

Nomolt, Dart, Diaract.

This is another haloaromatic substituted urea insecticide, apparently similar in toxicologic properties to diflubenzuron (above). Low systemic toxicity is reported.

CHLOROBENZILATE

STRUCTURE



COMMERCIAL PRODUCTS

Acaraben, Akar, Folbex, Benzilan.

Chlorobenzilate is a chlorinated hydrocarbon acaricide, usually formulated as an emulsion or wettable powder for application in orchards. It is presently a Restricted Use Pesticide because of neoplastic effects observed in laboratory animals subjected to high dosage over long periods.

TOXICOLOGY OF CHLOROBENZILATE

Chlorobenzilate is moderately irritating to the skin and eyes.

Although structurally similar to DDT, chlorobenzilate is much more rapidly excreted following absorption, chiefly in the urine as the benzophenone and benzoic acid derivatives. No systemic poisonings of humans have been reported. Based on observation of dosed animals, extreme absorbed doses may cause tremors, ataxia, and muscle weakness.

Chlorobenzilate is not a cholinesterase inhibitor.

TREATMENT OF CHLOROBENZILATE EXPOSURE

Remove skin contamination by washing with soap and water. Remove eye contamination by flushing with clean saline or water. If irritation persists, medical attention must be obtained.

If a large amount of chlorobenzilate was ingested within a few hours prior to treatment, and if there are no indications of central nervous system disturbance, empty the stomach by administering Syrup of Ipecac followed by several glasses of water. Dosage for adults and children over 12 years: 30 ml; dosage for children under 12 years: 15 ml.

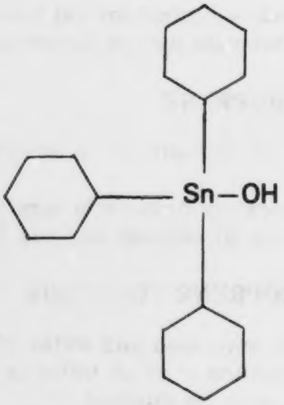
After vomiting stops, administer activated charcoal and sorbitol orally (for dosage, see Chapter 1, TREATMENT, Section 6, p. 8).

If there are indications of central nervous system disturbance (depression, ataxia, tremor), empty the stomach by intubation, aspiration, and lavage, after first taking all precautions to protect the respiratory tract from aspiration of gastric contents (see Chapter 1, TREATMENT, Section 6, p. 8). Lavage the stomach with a slurry of activated charcoal. Leave charcoal and an appropriate dose of sorbitol in the stomach before withdrawing the lavage tube.

If the absorbed dose of chlorobenzilate was small, if treatment is delayed, and if the patient is asymptomatic, oral administration of activated charcoal and sorbitol is probably the optimal management (see Chapter 1, TREATMENT, Section 6, p. 8 for dosage). Do not give fats or oils.

CYHEXATIN

STRUCTURE



COMMERCIAL PRODUCT

Plictran.

TOXICOLOGY OF CYHEXATIN AND TREATMENT OF TOXICOSIS

Tricyclohexyl tin hydroxide is formulated as a 50% wettable powder for control of mites on ornamentals, hops, nut trees and some fruit trees. It is moderately irritating, particularly to the eyes. While information on the systemic toxicity of this specific tin compound is lacking, it should probably be assumed that cyhexatin can be absorbed to some extent across the skin, and that substantial absorbed doses would cause nervous system injury (see Organotin compounds in Chapter 12: FUNGICIDES). Accordingly, dermal contamination should be promptly removed by washing with soap and water, and contamination of the eyes should be treated by prolonged flushing with clean water or saline. Management of poisonings by ingestion should proceed on the assumption that cyhexatin is highly toxic, even though rodent LD$_{50}$ values are fairly high, and no human poisonings have been reported. See Chapter 1, TREATMENT, Section 6, p. 8 concerning measures to limit toxicant absorption from the gut. Neither BAL, penicillamine nor chelating agents have been effective in lowering tissue stores of organic tin compounds in experimental animals.

METHOPRENE

COMMERCIAL PRODUCTS

ZR-515, Altosid SR-10 and CP-10, Apex 5E, Diacon, Dianex, Kabat, Minex, Pharorid, Precor.

Methoprene is a long chain hydrocarbon ester active as an insect growth regulator. It is effective against several insect species. Formulations include slow-release briquets, sprays, foggers and baits.

TOXICOLOGY OF METHOPRENE

Methoprene is neither an irritant nor a sensitizer in humans or laboratory animals.

Systemic toxicity in laboratory animals is very low. No human poisonings or adverse reactions in exposed workers have been reported.

TREATMENT OF METHOPRENE TOXICOSIS

Wash contaminated skin with soap and water. Flush contamination from eyes with copious amounts of clean water or saline. If irritation persists, medical attention must be obtained.

If a very large amount of methoprene has been ingested, oral administration of charcoal may be considered. The hazards of catharsis (dehydration, electrolyte disturbances) probably outweigh the hazards of methoprene.

SULFUR

$$S=S$$

COMMERCIAL PRODUCTS

Brimstone, Lacco Sulfur, Clifton Sulfur, Sul-Cide, Cosan, Kumulus S, Sofril, Sulfex. Thiolux, Thiovit, Magnetic 6, Liquid Sulfur, Thion, Zolvis, Golden Dew.

Elemental sulfur is an acaricide and fungicide widely used on orchard, ornamental, vegetable, grain and other crops. It is prepared as dust in various particle sizes and applied as such, or it is formulated with various minerals to improve flowability, or is applied as an aqueous emulsion or wettable powder.

TOXICOLOGY OF SULFUR

Elemental sulfur is moderately irritating to the skin, and airborne dust is irritating to the eyes and the respiratory tract. In hot sunny environments, there may be some oxidation of foliage-deposited sulfur to irritating gaseous sulfur oxides, which are very irritating to the eyes and respiratory tract.

Ingested sulfur powder induces catharsis, and has been used medicinally (usually with molasses) for that purpose. Some hydrogen sulfide is formed in the large intestine and this may present a degree of toxic hazard. However, an adult has survived ingestion of 60 grams.

Ingested colloidal sulfur is efficiently absorbed by the gut and is promptly excreted in the urine as inorganic sulfate.

TREATMENT OF SULFUR TOXICOSIS

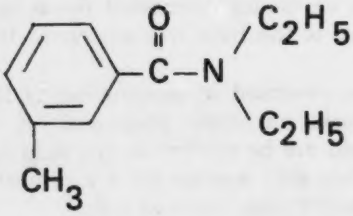
Skin contamination should be removed by washing with soap and water. Contamination of the eyes should be removed by prolonged flushing with clean saline or water. If irritation persists, medical attention should be obtained.

Unless an extraordinary amount of sulfur (several grams) has been ingested shortly prior to treatment, there is probably no need for emptying of the stomach or administration of a cathartic. Adsorbability of sulfur on activated charcoal has not been tested.

The most serious consequence of sulfur ingestion is likely to be that of catharsis: dehydration and electrolyte depletion, particularly in children. If diarrhea is severe, oral or intravenous administration of glucose and/or electrolyte solutions may be appropriate.

DIETHYLTOLUAMIDE (DEET)

STRUCTURE



COMMERCIAL PRODUCTS

Detamide, Metadelphene, MGK, OFF.

This chemical is a widely used liquid insect repellent, suitable for application to skin or to fabrics. It is formulated with ethyl or isopropyl alcohol, usually in pressurized containers.

TOXICOLOGY OF DEET

For many years, diethyltoluamide has been effective and generally well tolerated as an insect repellent applied to human skin, although tingling, mild irritation, and sometimes desquamation have followed repeated application. In some cases, DEET has caused contact dermatitis and excerbation of preexisting skin disease. It is very irritating to the eyes, but not corrosive.

Serious adverse effects have occurred when used under tropical conditions, when it was applied to areas of skin that were occluded during sleep (mainly the antecubital and popliteal fossae). Under these conditions, the skin became red and tender, then exhibited blistering and erosion, leaving painful weeping denuded areas that were slow to heal. Permanent scarring resulted from most of these severe reactions.

DEET is efficiently absorbed across the skin and by the gut. Blood concentrations of about 3 mg per liter have been reported several hours after dermal application in the prescribed fashion. Toxic encephalopathic reactions have apparently occurred in rare instances following dermal application, mainly in children who were intensively treated. The more frequent cause of systemic toxicity has been ingestion, deliberate in adults, accidental in young children.

Manifestations of toxic encephalopathy have been behavioral disorders including headache, restlessness, crying spells, mania, stupor progressing to coma, ataxia, hyperreflexia, tachypnea, hypotension, tremors, and writhing convulsions (athetosis). Some cases have shown flaccid paralysis and areflexia. Deaths have occurred following very large doses. Blood levels of DEET found in fatal systemic poisonings have ranged from 168 to 240 milligrams per liter. Interpretation of DEET toxicity in some fatal cases has been complicated by effects of simultaneously ingested ethanol, tranquilizers, and other drugs. One well documented case of anaphylactic reaction to DEET has been reported. One fatal case of encephalopathy in a child heterozygous for ornithine carbamoyl transferase deficiency resembled Reyes syndrome, but the postmortem appearance of the liver was not characteristic of the syndrome.

Discretion should be exercised in recommending DEET for persons who have acne, psoriasis, an atopic predisposition, or other chronic skin condition. It should not be applied to any skin area that is likely to be opposed to another skin surface for a significant period of time (antecubital and popliteal fossae, inguinal areas).

Great caution should be exercised in using DEET on children. Only the products containing the lower concentrations (usually 15%) should be used, and application should be limited to exposed areas of skin, using as little repellent as possible. If continuous repellent protection is necessary, DEET should be alternated with a repellent having another active ingredient. If headache or any kind of emotional or behavioral change occurs, use of DEET should be discontinued immediately.

CONFIRMATION OF DIETHYLTOLUAMIDE POISONING

Methods exist for measurement of DEET in blood and tissues and of metabolites in urine, but these are not widely available.

TREATMENT OF DEET TOXICOSIS

If a skin reaction occurs, residual DEET should be removed by washing the treated area with soap and water. Eye contamination should be treated by prolonged flushing with clean saline or water. If irritation persists, medical treatment should be obtained.

Steroid or antimicrobial topical medications may be indicated for severe skin reactions that occasionally follow application of DEET.

If a substantial amount of DEET has been **INGESTED** within a few hours of treatment, the stomach should be intubated, aspirated, and lavaged with a slurry of activated charcoal, after every precaution has been taken to protect the airway from aspiration of gastric contents (see Chapter 1, TREATMENT, Section 6, p. 8). A slurry of charcoal, including an appropriate dose of sorbitol, should be left in the stomach before the tube is withdrawn (see above reference for dosage). If a very large amount of DEET was swallowed, repeated doses of charcoal every 2–4 hours may be beneficial.

If dosage ingested was assuredly small, and the patient is fully alert, oral administration of activated charcoal and sorbitol probably represents optimal management. If diarrhea has already commenced, the sorbitol should be omitted.

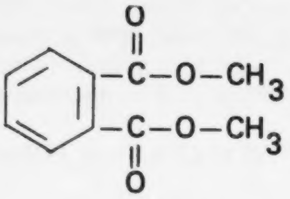
Intravenous electrolytes, plasma and/or whole blood may be needed to combat shock in severe poisonings. Administer oxygen continuously by mask if respiratory or circulatory embarrassment is evident. Adrenergic amines may be indicated.

If convulsive activity develops, benzodiazepine or other anticonvulsants may be required (see Chapter 3, TREATMENT, Section 4, p. 21).

Persons surviving poisoning by ingestion of DEET have usually recovered in 2 to 24 hours.

ALKYL PHTHALATES

STRUCTURE



DIMETHYL PHTHALATE

COMMERCIAL PRODUCT

DMP.

Dimethyl phthalate has been widely used as an insect repellent applied directly to the skin. Dibutylphthalate is impregnated into fabric for the same purpose. It is more resistant to laundering than dimethyl phthalate.

TOXICOLOGY OF ALKYL PHTHALATES

Dimethyl phthalate is strongly irritating to the eyes and mucous membranes. It has caused little or no irritation when applied to skin, and dermal absorption is apparently minimal. It has not caused sensitization.

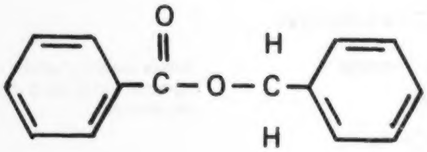
Tests in rodents have indicated low systemic toxicity, but large ingested doses cause gastrointestinal irritation, central nervous system depression (to coma), and hypotension. One accidental ingestion by a human resulted in coma, but recovery was prompt.

TREATMENT OF ALKYL PHTHALATE TOXICOSIS

No antidote is available. Supportive measures (hydration, oxygen if needed) are probably adequate to manage all but the most severe poisonings.

BENZYL BENZOATE

STRUCTURE



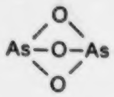
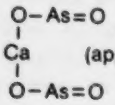
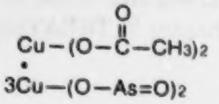
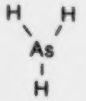
TOXICOLOGY, MANIFESTATIONS, AND TREATMENT

Incorporated into lotions and ointments, this agent has been used for many years in veterinary and human medicine against mites and lice. Apart from occasional cases of skin irritation, adverse effects have been few. The efficiency of skin absorption is not known. Absorbed benzyl benzoate is rapidly biotransformed to hippuric acid which is excreted in the urine. When given in large doses to laboratory animals, benzyl benzoate causes excitement, incoordination, paralysis of the limbs, convulsions, respiratory paralysis, and death. No human poisonings have been reported. If significant irritant effect appears, medication should be discontinued and the skin cleansed with soap and water. Eye contamination should be treated by prolonged flushing with clean water or saline. If a potentially toxic amount has been swallowed and retained, steps should be taken to remove it from the gastrointestinal tract and repeated doses of activated charcoal should be administered (see Chapter 1, TREATMENT, Section 6, p. 8). If seizures occur, control may require anticonvulsant medication (see Chapter 3, TREATMENT, Section 4, p. 21).

CHAPTER 6

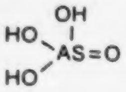
ARSENICAL PESTICIDES

INORGANIC TRIVALENT

Arsenic Trioxide 	"White arsenic," arsenous oxide. The active ingredient in some ant pastes and veterinary preparations.
Sodium arsenite $\mathrm{Na-O-As=O}$	Chem Pels C. Chem-Sen 56, Kill-All, Penite, Prodalumnol Double. Used in aqueous solution for weed control; limited use as insecticide.
Calcium arsenite  $\begin{array}{l} \mathrm{O-As=O} \\ \mid \\ \mathrm{Ca} \\ \mid \\ \mathrm{O-As=O} \end{array}$ (approx.)	Mono-calcium arsenite. Flowable powder for insecticidal use on fruit.
Copper arsenite (Acid copper arsenite) $\mathrm{HO-Cu-O-As=O}$	Wettable powder, for use as insecticide, wood preservative.
Copper acetoarsenite  $\mathrm{Cu-(O-\overset{O}{\overset{\Vert}{C}}-CH_3)_2 \cdot 3Cu-(O-As=O)_2}$	Insecticide. Paris Green, Schweinfurt green, emerald green, French green, mitis green. No longer used in U.S.; still used outside U.S.
Arsine 	Not a pesticide. Occasionally generated during manufacture of arsenicals.

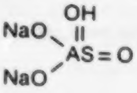
INORGANIC PENTAVALENT

Arsenic acid



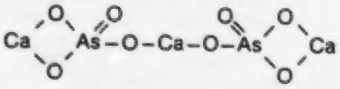
Dessicant L-10, Hi-Yield Dessicant H-10, Zotox. Water solutions used as defoliants, herbicides.

Sodium arsenate



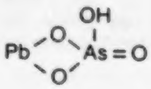
Disodium arsenate. Jones Ant Killer, Terro Ant Killer.

Calcium arsenate



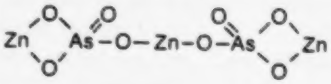
Tricalcium arsenate. Pencal, Spra-cal, Turf-Cal. Flowable powder formulations used against weeds, grubs.

Lead arsenate



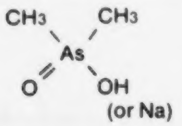
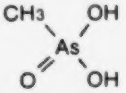
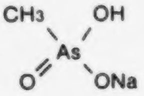
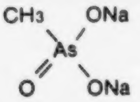
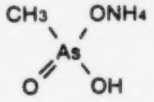
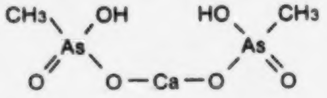
Gypsine, Soprabel, Talbot. Limited use in U.S.; wettable powder used as insecticide outside the U.S.

Zinc arsenate



Powder one used in U.S. as insecticide on potatoes and tomatoes.

ORGANIC (PENTAVALENT)

Cacodylic acid (sodium cacodylate) 	Non-selective herbicide, defoliant, silvicide. Bolate, Bolls-Eye, Bophy, Dilie, Kack, Phytar 560, Rad-E-Cate 25, Salvo.
Methane arsonic acid 	MAA. Non-selective herbicide.
Monosodium methane arsonate 	MSMA. Non-selective herbicide, defoliant, silvicide. Ansar 170, Arsonate Liquid, Bueno 6, Daconate 6, Dal-E-Rad, Drexar 530, Herb-All, Merge 823, Mesamate, Target MSMA, Trans-Vert, Weed-E-Rad, Weed-Hoe.
Disodium methane arsonate 	DSMA. Selective post-emergence herbicide, silvicide. Ansar 8100, Arrhenal, Arsinyl, Crab-E-Rad, Di-Tac, DMA, Methar 30, Sodar, Weed-E-Rad 360.
Monoammonium methane arsonate 	MAMA. Selective post-emergence herbicide.
Calcium acid methane arsonate 	CAMA. Selective post-emergence herbicide. Calar, Super Crab-E-Rad-Calar, Super Dal-E-Rad.

SOLID ARSENIC COMPOUNDS

TOXICOLOGY OF ARSENIC

Arsenic is a natural element having both metal and nonmetal physical/chemical properties. In one respect or another, it resembles nitrogen, phosphorus, antimony, and bismuth in its chemical behavior. In nature, it exists in elemental, trivalent (−3 or +3), and pentavalent (+5) states. It binds covalently with most nonmetals (notably oxygen and sulfur) and with metals (for example, calcium and lead). It forms stable trivalent and pentavalent organic compounds. In biochemical behavior, it resembles phosphorus, competing with phosphorus analogs for chemical binding sites. Toxicity of the various arsenic compounds in mammals extends over a wide range, determined, in part, by unique biochemical actions of each compound, but also by absorbability and efficiency of biotransformation and disposition. Overall, arsines present the greatest toxic hazard, followed closely by arsenites (inorganic trivalent compounds). Inorganic pentavalent compounds are somewhat less toxic that arsenites, while the organic (methylated) pentavalent compounds incur the least hazard of the arsenicals that are used as pesticides.

The pentavalent arsenicals are relatively water soluble and absorbable across mucous membranes while trivalent arsenicals, having greater lipid solubility, are more readily absorbed across the skin. However, poisonings by dermal absorption of either form have been extremely rare. Ingestion has been the usual basis of poisoning; gut absorption efficiency depends on the physical form of the compound, its solubility characteristics, the gastric pH, gastrointestinal motility, and gut microbial transformations. Once absorbed, many arsenicals cause toxic injury to cells of the nervous system, blood vessels, liver, kidney, and other tissues. Two biochemical mechanisms of toxicity are recognized: 1) reversible combination with thiol groups contained in tissue proteins and enzymes, and 2) substitution of arsenic anions for phosphate in many reactions, including those critical to oxidative phosphorylation. Because there are many uncertainties regarding the biotransformation of various arsenicals in the gut and in the body, and because the toxic potentials of the biotransformation products are not well established, it is generally safest to manage cases of arsenic ingestion as though all forms of arsenic are highly toxic.

Mammals, including humans, detoxify inorganic arsenic by methylation, yielding cacodylic acid (dimethylarsinic acid) as the chief urinary excretion product. Disposition by urinary excretion is usually prompt. Elimination of the arsonic acid (monomethyl) compounds has not been extensively studied, but urinary excretion of the unaltered compound and/or a further methylated form would seem likely.

The unique toxicology of arsine gas is described later in this chapter.

SYMPTOMS AND SIGNS OF POISONING BY SOLID ARSENICALS

Manifestations of acute poisoning (large amount absorbed over a short time) are distinguishable from those of chronic poisoning (lesser doses absorbed over a longer time interval).

The symptoms and signs of ACUTE ARSENIC POISONING usually appear within one hour after ingestion, but may be delayed several hours. **GARLIC ODOR** of the breath and feces may help to identify the responsible toxicant in a severely poisoned patient. Gastrointestinal effects include inflammation of the mouth, pharynx, and esophagus, burning abdominal pain, thirst, vomiting, and rice-water or bloody diarrhea. These effects result from the action of an arsenical metabolite on blood vessels generally, but the splanchnic vasculature particularly, causing dilation and increased capillary permeability.

Renal injury is manifest as proteinuria, hematuria, glycosuria, oliguria, casts in the urine, and, in severe poisoning, acute tubular necrosis. Central nervous system effects include headache, dizziness, muscle weakness and spasms, hypothermia, lethargy, delirium, coma, and convulsions. Cardiovascular manifestations include shock, cyanosis, and cardiac arrhythmias, which are due to direct toxic action and electrolyte disturbances. Liver damage may lead to increased concentrations of circulating hepatocellular enzymes and to jaundice. Injury to blood-forming tissues may cause anemia, leukopenia, and thrombocytopenia. Death usually occurs one to three days following symptom onset and is usually the result of circulatory failure.

CHRONIC ARSENIC POISONING from repeated absorption of toxic amounts generally has an insidious onset of clinical effects and may be difficult to diagnose. Dermal manifestations are usually more prominent than the gastrointestinal effects which characterize acute poisoning: hyperkeratosis, hyperpigmentation, exfoliative dermatitis, subcutaneous edema of the face, eyelids and ankles, white striations across the nails (Mees lines), and sometimes loss of nails or hair. Stomatitis, anorexia, and weight loss are typical. Peripheral neuropathy (paresthesia, pain, anesthesia, paresis, ataxia) may be a prominent feature. Liver injury reflected in hepatomegaly and jaundice may progress to cirrhosis, portal hypertension, and ascites. Nephropathy is indicated principally by proteinuria. Electrocardiographic abnormalities and peripheral vascular disease have been reported. Anemia, leukopenia, and thrombocytopenia are characteristic. Late sequelae of protracted high intakes of arsenic include skin cancer, an increased risk of lung cancer, and, rarely, encephalopathy (ophthalmoplegia, chronic headache, speech and mental disturbances).

CONFIRMATION OF POISONING BY ARSENICALS

Measurement of 24-hour urinary excretion of arsenic (micrograms per day) is probably the best way to confirm excessive absorption, although methods for blood arsenic concentration are available (see below). Persons on non-seafood diets usually excrete less than 20 micrograms (mcg) per day, but diets rich in seafood may generate as much as 200 mcg per day and sometimes more. (The arsenic in seafood is apparently bound firmly to betaine, which renders the arsenic essentially nontoxic and highly excretable.) Arsenic excretion above 100 mcg per day should be viewed with suspicion and the test should be repeated. Excretions above 200 mcg per day reflect a toxic intake, unless seafood was ingested.

In acute poisonings that require a prompt indication as to whether recent arsenic intake has been far in excess of normal, two qualitative tests of urine are generally available, both sensitive to concentrations of about 2000 mcg per liter of urine:

> Gutzeit test: To 5 ml of urine, add a few drops of concentrated sulfuric acid and a few granules of elemental zinc. Cover the top of the tube with a piece of filter paper to which a drop or two of 1% silver nitrate solution has been added. Browning or blackening of the paper indicates that arsine has been evolved from the urine.
>
> Reinsch test: Concentrate 10 ml of urine to 1 ml by boiling. Prepare a piece of copper foil or wire by cleaning the surface, then treating it with concentrated nitric acid, then washing it with distilled water. Put the copper in a flask with the concentrated urine sample and acidify with about 0.1 ml concentrated hydrochloric acid. Boil for 15 minutes. A dull black stain probably indicates arsenic. Bismuth, mercury, and antimony cause somewhat different discolorations of the copper. If this occurs, analysis for arsenic specifically must be carried out.

Lower concentrations of arsenic in blood, urine, or other biologic materials can be measured by either wet or dry ashing, followed by colorimetric or atomic absorption spectrometric analysis. (Baselt, R.C. Biological Monitoring Methods for Industrial Chemicals, Biomedical Publications, 1980.) Blood concentrations in excess of about 100 mcg per liter probably indicate excessive intake, if seafood was not ingested before the sample was taken.

Special tests for arsine toxicosis are described below under "Arsine Gas."

TREATMENT OF ARSENIC COMPOUND TOXICOSIS

The following discussion applies principally to poisonings by arsenicals that are in solid or dissolved form. Treatment of poisoning by arsine gas requires special measures that are described later in this chapter under "Arsine Gas."

1. Wash arsenical pesticide from skin and hair with copious amounts of soap and water.
2. Flush contaminant from eyes with clean water. If irritation persists, specialized medical treatment should be obtained.
3. If arsenical pesticide has been ingested within a few hours of treatment, empty the stomach by **INTUBATION, ASPIRATION,** and **LAVAGE,** taking all precautions to protect the respiratory tract from aspiration of vomitus. The effectiveness of gastric evacuation diminishes rapidly with the passage of time. The procedure for evacuation of the stomach is described in Chapter 1, TREATMENT, Section 6, p. 8.
4. Leave activated charcoal in the stomach, as indicated in the above reference. Repeated administration of charcoal at half or more the original dose every 2–4 hours may be beneficial.
5. Because poisoning by ingested arsenic almost always results in profuse diarrhea, it is generally **NOT** appropriate to **ADMINISTER a CATHARTIC.**
6. If treatment has been delayed, and if the victim remains fully alert, administer activated charcoal orally at dosages suggested in Chapter 1, TREATMENT, Section 6. Repeat every 2–4 hours.
7. Administer **INTRAVENOUS FLUIDS** to restore adequate hydration, support urine flow, and correct electrolyte imbalances. Monitor intake/output continuously to guard against fluid overload if acute renal failure occurs. Monitor blood electrolytes regularly. Blood transfusions and oxygen by mask may be needed to combat shock.
8. Monitor cardiac status by ECG to detect arrhythmias and toxic myocardiopathy (T wave inversion, long S-T interval).
9. Administration of **DIMERCAPROL (BAL)** is usually indicated in symptomatic arsenic poisonings. The following dosage schedule has proven to be effective in accelerating arsenic excretion.

Recommended Intramuscular Dosage of BAL (Dimercaprol) in Arsenic Poisoning

	Severe Poisoning	Mild Poisoning
1st day	3.0 mg/kg q4h (6 injections)	2.5 mg/kg q6h (4 injections)
2nd day	3.0 mg/kg q4h (6 injections)	2.5 mg/kg q6h (4 injections)
3rd day	3.0 mg/kg q6h (4 injections)	2.5 mg/kg q12h (2 injections)
Each of the following days for 10 days, or until recovery	3.0 mg/kg q12h (2 injections)	2.5 mg/kg qd (1 injection)

BAL is provided as a 100 mg/ml solution in oil. Dosages in the table are in terms of BAL itself, not of the solution.

CAUTION: Disagreeable side effects often accompany the use of BAL: nausea, headache, burning and tingling sensations, sweating, pain in the back and abdomen, tremor, restlessness, tachycardia, hypertension, and fever. Coma and convulsions occur at very high dosage. Sterile abscesses may form at injection sites. Acute symptoms usually subside in 30-90 minutes. Antihistamine drugs or an oral dose of 25-50 mg ephedrine sulfate provide relief. These are more effective if given a few minutes before the injection of BAL.

10. After the gastrointestinal tract is reasonably free of arsenic (as indicated by passage of a charcoal-black stool), oral administration of **D-PENICILLAMINE** should probably replace BAL therapy in persons who are not allergic to penicillin.

    Dosage of D-PENICILLAMINE:

    Adults and children over 12 years: 0.5 gm every 6 hours, given 30-60 minutes before meals and at bedtime for about 5 days.

    Children under 12 years: 0.1 gm/kg body weight, not exceeding 1.0 gm per day, divided into 4 doses, given 30-60 minutes before meals and at bedtime for about 5 days.

    CAUTION: Adverse reactions to short term therapy are rare. Persons allergic to penicillin may suffer allergic reactions to D-penicillamine; they should be treated with BAL only.

11. Extracorporeal hemodialysis, used in combination with BAL therapy, has limited effectiveness in removing arsenic from the blood. Hemodialysis is clearly indicated to enhance arsenic elimination and maintain extracellular fluid composition if acute renal failure occurs.

12. **MONITOR URINARY ARSENIC EXCRETION** while BAL or D-penicillamine are being administered. When 24-hour excretion falls below 50 mcg per day, it is usually advisable to discontinue the chelation therapy.

ARSINE GAS

Arsine is not used as a pesticide. However, some poisonings by arsine have occurred in pesticide manufacturing plants and metal refining operations when arsenicals came into contact with mineral acids or strong reducing agents.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY ARSINE

Arsine is a powerful **HEMOLYSIN**, a toxic action not exhibited by other arsenicals. In some individuals, very little inhalation exposure is required to cause a serious hemolytic reaction. Symptoms of poisoning usually appear 1-24 hours after exposure: headache, malaise, weakness, dizziness, dyspnea, nausea, **ABDOMINAL PAIN**, and vomiting. Dark red urine (**HEMOGLOBINURIA**) is often passed 4–6 hours after exposure. Usually 1–2 days after hemoglobinuria appears, **JAUNDICE** is evident. Hemolytic anemia, sometimes profound, usually provides diagnostic confirmation and can cause severe weakness. Abdominal tenderness and liver enlargement are often apparent. Basophilic stippling of red cells, red cell fragments, and ghosts are seen in the blood smear. Methemoglobinemia and methemoglobinuria are evident. Elevated concentrations of arsenic are found in the urine, but these are not nearly as high as are found in poisonings by solid arsenicals. Plasma content of unconjugated bilirubin is elevated.

Renal failure due to direct toxic action of arsine and to products of hemolysis represents the chief threat to life in arsine poisoning.

Polyneuropathy and a mild psycho-organic syndrome are reported to have followed arsine intoxication after a latency of 1–6 months.

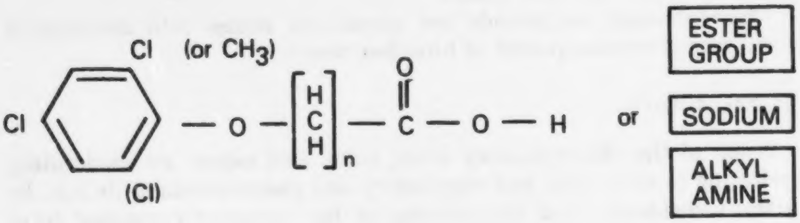
TREATMENT OF ARSINE TOXICOSIS

1. Remove the victim to fresh air.
2. Administer **INTRAVENOUS FLUIDS** to keep the urine as dilute as possible and to support excretion of arsenic and products of hemolysis. Include sufficient sodium bicarbonate to keep the urine alkaline (pH greater than 7.5).
   CAUTION: Monitor fluid balance carefully to avoid fluid overload if renal failure supervenes. Monitor plasma electrolytes to detect disturbances (particularly hyperkalemia) as early as possible.
3. Monitor urinary arsenic excretion to assess severity of poisoning. The amount of arsine that must be absorbed to cause poisoning is small, and therefore high levels of urinary arsenic excretion should not be expected, even in severe poisoning.
4. If poisoning is severe, **EXCHANGE BLOOD TRANSFUSION** may be considered. It was successful in rescuing one adult victim of arsine poisoning.
5. Extracorporeal **HEMODIALYSIS** may be necessary to maintain normal extracellular fluid composition and to enhance arsenic elimination if renal failure occurs, but it is not very effective in removing the arsine carried in the blood.
6. Administration of BAL (dimercaprol) may be considered, but it has not proven to be effective in arsine poisonings to date. The efficacy of D-penicillamine has not been tested.

CHAPTER 7

CHLOROPHENOXY HERBICIDES

GENERAL CHEMICAL STRUCTURE



COMMERCIAL PRODUCTS

Several hundred commercial products contain chlorophenoxy herbicides in various forms, concentrations, and combinations. Following are names of widely advertised formulations. In some cases, the same name is used for products with different ingredients. Exact composition must therefore be determined from the product label.

2,4-D or 2,4-dichlorophenoxyacetic acid (Agrotect, Amoxone, Aqua-Kleen, BH 2,4-D, Chipco Turf Herbicide 'D', Chloroxone, Crisalamina, Crisamina, Crop Rider, D50, Dacamine, Debroussaillant 600, Ded-Weed SULV, Desormone, Dinoxol, Emulsamine BK, Emulsamine E-3, Envert DT, Envert 171, Super D Weedone, Weedone, Estone, Farmco, Fernesta, Fernimine, Fernoxone, Ferxone, Formula 40, Gordon's Amine 400, Gordon's LV 400 2,4-D, Hedonal, Herbidal, Lawn-Keep, Macondray, Miracle, Netagrone 600, Pennamine D, Planotox, Plantgard, Salvo, Spritz-Hormin/2,4-D, Spritz-Hormit/2,4-D, Superormone Concentre, Transamine, Tributon, Tuban, U 46, U 46 D-Ester, U 46 D-Fluid, Weed-B-Gon, Weedar, Weedatul, Weed-Rhap, Weed Tox, Weedtrol, Gordon's Dymec Turf Herbicide Amine 2,4-D, Gordon's Phenaban 801, Acme Amine 4, Acme Butyl Ester 4, Acme LV 6, Acme LV 4, Gordon's Butyl Ester 600, DMA 4, Dormone).

2,4-DP or 2,4-dichlorophenoxypropionic acid (BH 2,4-DP, Desormone, Hedonal, Hedonal DP, Kildip, Polymone, Seritox 50, U 46, U 46 DP-Fluid, Weedone DP, Weedone 170).

2,4-DB or 2,4-dichlorophenoxybutyric acid (Butoxon, Butoxone, Butyrac, Embutox).

2,4,5-T or 2,4,5-trichlorophenoxyacetic acid (Amine 2,4,5-T for rice, Dacamine, Ded-Weed, Farmco Fence Rider, Forron, Inverton 245, Line Rider, Super D Weedone, T-Nox, Trinoxol, U 46, Weedar, Weedone).

MCPA (metaxon, Agroxone, Weedone), MCPB (Can-Trol, PDQ, Thistrol), and MCPP (mecoprop, Methoxone M, Mecopex, Gordon's Mecomec) are 2-methyl, 4-chlorophenoxy aliphatic acids and esters.

Dicamba (Banvel) is 2-methyl-3,6 dichlorobenzoic acid.

Sodium, potassium, and alkylamine salts are commonly formulated as aqueous solutions, while the less water soluble esters are applied as emulsions. Low molecular weight esters are more volatile than the acids, salts, or long-chain esters.

Chlorophenoxy compounds are sometimes mixed into commercial fertilizers to control growth of broadleaf weeds.

TOXICOLOGY

Some of the chlorophenoxy acids, salts, and esters are moderately irritating to skin, eyes, and respiratory and gastrointestinal linings. In a few individuals, local depigmentation has apparently resulted from protracted dermal contact with chlorophenoxy compounds.

The chlorophenoxy compounds are absorbed across the gut wall, lung, and skin. They are not significantly fat storable. Excretion occurs almost entirely by way of the urine. Apart from some conjugation of the acids, there is limited biotransformation in the body. The average residence half-life of 2,4-D in the human is about 18 hours, that of 2,4,5-T about 24 hours. These averages lie within very wide ranges (4-140 hours in the case of 2,4-D), depending on urinary pH (alkalinity enhances excretion).

Given in large doses to experimental animals, 2,4-D causes vomiting, diarrhea, anorexia, weight loss, ulcers of the mouth and pharynx, and toxic injury to the liver, kidneys, and central nervous system. Myotonia (stiffness and incoordination of hind extremities) develops in some species and is apparently due to CNS damage: demyelination has been observed in the dorsal columns of the cord, and EEG changes have indicated functional disturbances in the brains of heavily dosed experimental animals.

Ingestion of large amounts of chlorophenoxy acids has resulted in severe metabolic acidosis in humans. Such cases have been associated with electrocardiographic changes, myotonia, muscle weakness, myoglobinuria, and elevated serum creatine phosphokinase, all reflecting injury to striated muscle. Because chlorophenoxy acids are weak uncouplers of oxidative phosphorylation, extraordinary doses may produce hyperthermia from increased production of body heat.

Chlorinated Dibenzo Dioxin (CDD) and Chlorinated Dibenzo Furan (CDF) compounds are generated in the manufacture of chlorophenoxy compounds, particularly at excessive temperatures. The 2,3,7,8-tetra CDD form is extraordinarily toxic to multiple mammalian tissues; it is formed only in the synthesis of 2,4,5-T. Hexa-, hepta-, and octa-compounds exhibit less systemic toxicity, but are the likely cause of chloracne (a chronic, disfiguring skin condition) seen in workers engaged in the manufacture of 2,4,5-T and certain other chlorinated organic compounds. Although toxic effects, notably chloracne, have been observed in manufacturing plant workers, these effects have not been observed in formulators or applicators regularly exposed to 2,4,5-T or other chlorophenoxy compounds.

The medical literature contains some reports of peripheral neuropathy following what seemed to be minor dermal exposures to 2,4-D. It is not certain that exposures to other neurotoxicants were entirely excluded in these cases. Single doses of 5 mg/kg body weight of 2,4-D and 2,4,5-T have been administered to human subjects without any adverse effects. One subject consumed 500 mg of 2,4-D per day for 3 weeks without experiencing symptoms or signs of illness.

SYMPTOMS AND SIGNS OF POISONING

Chlorophenoxy compounds are moderately **IRRITATING** to skin and mucous membranes. Inhalation of sprays may cause burning sensations in the nasopharynx and chest and coughing may result. Prolonged inhalation sometimes causes dizziness. Adjuvant chemicals added to enhance foliage penetration may account for the irritant effects of some formulations.

Manifestations of systemic toxicity of chlorophenoxy compounds are known mainly from clinical experience with cases of deliberate suicidal ingestion of large quantities. The agents most often involved in these incidents have been 2,4-D and mecoprop. The toxic effects of other chlorophenoxy compounds are probably similar but not identical. Few cases of deliberate ingestion of chlorophenoxy compounds have terminated fatally.

Irritation of the stomach usually leads to **VOMITING** soon after ingestion. Pain in the chest and abdomen and diarrhea may ensue. Headache, mental confusion, and bizarre behavior are early manifestations of severe poisoning which may progress to **UNCONSCIOUSNESS. MYOTONIA** (muscular stiffness on passive movement of the limbs) has occurred in persons poisoned by 2,4-D. Areflexia is sometimes observed. Muscle twitching may or may not be evident. Convulsions occur very rarely. Respiratory drive is not depressed; hyperventilation is sometimes evident. Body temperature may be moderately elevated, but this is rarely a life-threatening feature of the poisoning. With effective urinary excretion of the toxicant, consciousness usually returns in 48–96 hours.

Metabolic acidosis is manifest as a low arterial pH and bicarbonate content. The urine is usually acid. Skeletal muscle injury, if it occurs, is reflected in elevated creatine phosphokinase, and sometimes myoglobinuria. Moderate temporary elevations of blood urea nitrogen and serum creatinine are commonly found as the toxicant is excreted, but acute renal failure is uncommon. Mild leukocytosis and biochemical changes indicative of liver cell injury have been reported. Both tachycardia and bradycardia have been observed. T-wave flattening and inversion may occur.

Myotonia and muscle weakness may persist for months after acute poisoning. Electromyographic and nerve conduction studies in some recovering patients have demonstrated a mild proximal neuropathy and myopathy.

CONFIRMATION OF POISONING

Gas-liquid chromatographic methods are available for detecting and measuring chlorophenoxy compounds in blood and urine. These analyses are useful in confirming and assessing the magnitude of chlorophenoxy absorption. Poisonings characterized by unconsciousness have shown initial blood chlorophenoxy concentrations ranging from 80 to more than 1000 mg per liter. Urine samples should be collected as soon as possible after exposure because the herbicides may be almost completely excreted in 24–72 hours, depending on the extent of toxicant absorption and urine pH. Analyses can be performed at special laboratories usually known to local poison control centers. If circumstances indicate strongly that excessive exposure to chlorophenoxy compounds has occurred, **INITIATE** appropriate **TREATMENT** measures immediately, not waiting for chemical confirmation of toxicant absorption.

TREATMENT OF POISONING BY CHLOROPHENOXY COMPOUNDS

1. **BATHE and SHAMPOO** with soap and water to remove chemicals from skin and hair. Obtain medical treatment if irritation persists. Individuals with chronic skin disease or known sensitivity to these herbicides should either avoid using them or take strict precautions to avoid contact (respirator, gloves, etc.).
2. **FLUSH** contaminating chemicals from eyes with copious amounts of clean water for 10–15 minutes. If irritation persists, obtain medical treatment.
3. If any symptoms of illness occur during or following inhalation of spray, **REMOVE** victim **FROM CONTACT** with the material for at least 2–3 days. Allow subsequent contact with chlorophenoxy compounds only if effective respiratory protection is practiced.
4. If substantial amounts of chlorophenoxy compounds have been **INGESTED**, spontaneous emesis may occur. If vigorous emesis has not occurred, measures should be taken to empty the stomach and limit gastrointestinal absorption by **GASTRIC INTUBATION, ASPIRATION,** and **LAVAGE**, following placement of a cuffed endotracheal tube. Lavage procedure is described in Chapter 1, **TREATMENT**, Section 6, page 8. Repeated administration of charcoal at half or more the original dosage every 2–4 hours may be beneficial.

If gastric aspiration and lavage is not performed due to delay in treatment, and if the patient is fully alert, **ADMINISTER CHARCOAL AND LAXATIVE ORALLY**, at the dosages indicated in Chapter 1, TREATMENT, Section 6, p. 8.

5. Administer **INTRAVENOUS FLUIDS** to accelerate excretion of the chlorophenoxy compound, and to limit concentration of the toxicant in the kidney. A urine flow of 4–6 ml/minute is desirable. Intravenous saline/dextrose has sufficed to rescue comatose patients who drank 2,4-D and mecoprop several hours before hospital admission.

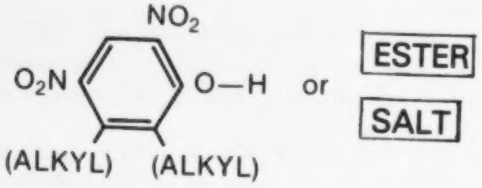
   CAUTION: Monitor urine protein and cells, BUN, serum creatinine, serum electrolytes, and fluid intake/output carefully to insure that renal function remains unimpaired and that fluid overload does not occur.

   Forced **ALKALINE DIURESIS** has been used successfully in management of suicidal ingestions of chlorophenoxy compounds. Alkalinizing the urine by including sodium bicarbonate (44–88 mEq per liter) in the intravenous solution apparently accelerates excretion of 2,4-D dramatically and mecoprop excretion substantially. Urine pH should by maintained in the 7.6–8.8 range. Include potassium chloride as needed to offset increased potassium losses: add 20–40 mEq of potassium chloride to each liter of intravenous solution. Monitor serum electrolytes carefully. There may possibly be some hazard to the kidneys when urine concentrations of toxicant are very high, so the integrity of renal function and fluid balance should be monitored carefully as the chlorophenoxy compound is excreted.
6. Hemodialysis is not likely to be of significant benefit in poisonings by chlorophenoxy compounds because of the extensive protein binding of these chemicals.
7. Follow-up clinical examination should include electromyographic and nerve conduction studies to detect any neuropathic changes and neuromuscular junction defects.

CHAPTER 8

NITROPHENOLIC AND NITROCRESOLIC HERBICIDES

GENERAL CHEMICAL STRUCTURE



COMMERCIAL PRODUCTS

Dinitrophenol (Chemox PE), dinitrocresol (DNOC, DNC, Chemsect DNOC, Elgetol 30, Nitrador, Selinon, Sinox, Trifocide), dinoseb (DNBP, dinitro, Basanite, Caldon, Chemox General, Chemox PE, Chemsect DNBP, Dinitro, Dinitro-3, Dinitro General, Dynamyte, Elgetol 318, Gebutox, Hel-Fire, Kiloseb, Nitropone C, Premerge 3, Sinox General, Subitex, Unicrop DNBP, Vertac, Dinitro Weed Killer 5, Vertac General Weed Killer, Vertac Selective Weed Killer), dinoseb acetate (Aretit), dinoseb methacrylate (binapacryl, Morocide, Acricid, Ambox, Dapacryl, Endosan, FMC 9044, Hoe 002784, Morrocid, NIA 9044), dinosulfon, dinoterbon, dinoterb acetate, dinoterb salts, dinosam (DNAP, Chemox General), dinoprop, dinocap (Crotothane, Karathane), dinobuton (Acrex, Dessin, Dinofen, Drawinol, Talan), dinopenton.

These agents have many uses in agriculture worldwide: herbicides (weed-killing and defoliation), acaricides, nematocides, ovicides, fungicides. Relatively insoluble in water, most technical products are dissolved in organic solvents and are formulated for spray application as emulsions. There are some wettable powder formulations.

TOXICOLOGY

Nitroaromatic compounds are highly toxic to humans and animals. Most nitrophenols and nitrocresols are well absorbed from the gastrointestinal tract, across the skin, and by the lung when fine droplets are inhaled. Fatal poisonings have occurred as a result of dermal contamination. Except in a few sensitive individuals, they are only moderately irritating to the skin and mucous membranes.

Nitrophenols and nitrocresols undergo some biotransformation in humans, chiefly reduction (one nitro group to an amino group) and conjugation at the phenolic site. Although nitrophenols and metabolites appear consistently in the urine of poisoned individuals, hepatic excretion is probably the main route of disposition. Elimination is slow: residence half-life in humans is 5–14 days. Blood and tissue concentrations tend to increase progressively if an individual is substantially exposed on successive days.

Nitrophenols and nitrocresols are toxic to the liver, kidney, and nervous system. The basic mechanism of toxicity is stimulation of oxidative metabolism in cell mitochondria, by interference with the normal coupling of carbohydrate oxidation to phosphorylation (ADP to ATP). The nitrophenols are more active as uncouplers than chlorophenols. Increased oxidative metabolism leads to hyperthermia, tachycardia, and dehydration, and in time, depletes carbohydrate and fat stores. Most severe occupational poisonings from absorption of these compounds have occurred in workers laboring in hot environments. Hyperthermia and direct action on the brain cause cerebral edema, manifest clinically as a toxic psychosis and sometimes convulsions. Liver parenchyma and renal tubules show degenerative changes. Albuminuria, pyuria, hematuria, and azotemia are signs of renal injury.

Neutropenia has occurred in humans following heavy exposure to dinitrophenol. Cataracts occur in laboratory animals given nitrophenols, and have occurred in humans, both as a result of ill-advised medicinal use and as a consequence of occupational exposure. Cataract formation is sometimes accompanied by glaucoma.

SYMPTOMS AND SIGNS OF POISONING

Yellow staining of skin and hair often signify topical contact with a nitroaromatic chemical. Staining of the sclerae and urine indicate absorption of potentially toxic amounts. Profuse **SWEATING, THIRST, FEVER, HEADACHE**, confusion, malaise, and lassitude are common early symptoms of poisoning. Warm flushed skin, tachycardia, and tachypnea indicate a serious degree of poisoning. **RESTLESSNESS**, apprehension, anxiety, manic behavior, or unconsciousness reflect cerebral injury. **CONVULSIONS** signify an immediately life-threatening intoxication. Labored breathing and cyanosis are consequences of the stimulated metabolism and tissue anoxia. Weight loss occurs in persons continually exposed to relatively low doses of nitrophenols or nitrocresols.

CONFIRMATION OF POISONING

Unmetabolized nitrophenols and nitrocresols can be identified spectrophotometrically, or by gas-liquid chromatography, in the serum and urine at concentrations well below those that have been associated with acute poisonings. Blood analysis is useful in confirming the cause of poisoning, but has little value in monitoring progress or predicting outcome. If poisoning is probable, **DO NOT AWAIT CONFIRMATION** before commencing treatment, but save urine and blood specimens in the event confirmation is necessary later on.

TREATMENT OF NITROPHENOL OR NITROCRESOL POISONING

1. If poisoning has been caused by contamination of body surfaces, **BATHE** and **SHAMPOO** contaminated **SKIN** and **HAIR** promptly and thoroughly with soap and water, or water alone if soap is not available. Wash the chemical from skin folds and from under fingernails. **CONTAMINATED CLOTHING** should be promptly removed, bagged, and not returned until it has been thoroughly laundered. Contaminated leather shoes should be discarded. The possibility that pesticide has contaminated the inside surfaces of gloves, boots, and headgear should be kept in mind.
2. **FLUSH** chemical from **EYES** with copious amounts of clean water. Obtain medical attention if irritation or other injury persists.
3. Systemic poisoning must be treated by controlling body temperature, providing oxygen, maintaining hydration, and relieving agitation.
   A. **REDUCE ELEVATED BODY TEMPERATURE BY PHYSICAL MEANS.** Administer sponge baths and cover victim with cool blankets. In fully conscious patients, administer cold, sugar-containing liquids by mouth as tolerated.
   B. **DO NOT** administer atropine, aspirin, or other salicylates to control hyperthermia. These agents appear likely to enhance the toxicity of phenolic substances. Neither the safety nor the effectiveness of other antipyretics has been tested.
   C. Administer **OXYGEN** continuously by mask to minimize tissue anoxia.
   D. Unless there are manifestations of cerebral or pulmonary edema or of inadequate renal function, administer **INTRAVENOUS FLUIDS** to restore hydration and support physiologic mechanisms for heat loss and toxicant disposition. Monitor serum electrolytes, adjusting IV infusions to stabilize electrolyte concentrations. Follow urine contents of albumin and cells, and keep an accurate hourly record of intake/output to forestall fluid overload if renal function declines.
   CAUTION: In the presence of cerebral edema and/or impaired renal function, intravenous fluids must be administered very cautiously to avoid increased intracranial pressure and pulmonary edema.

E. In severe poisonings, monitor pulmonary ventilation carefully to insure adequate gas exchange, and monitor cardiac status by ECG to detect arrhythmias. The toxicant itself and severe electrolyte disturbances may predispose to arrhythmias and myocardial weakness.

F. To reduce production of heat in the body, **CONTROL AGITATION** and involuntary motor activity with sedatives. **DIAZEPAM** or other benzodiazepine should be effective, although use of these drugs in nitroaromatic poisoning has not been reported. If diazepam is chosen, administer **SLOWLY**, intravenously.

Dosage of **DIAZEPAM**:

> **Adults and children over 12 years:** 5–10 mg. Repeat if necessary to a maximum of 30 mg.
>
> **Children under 12 years:** 0.25–0.40 mg/kg body weight. Repeat if necessary to a maximum of 10 mg for children 5–12 years and to a maximum of 5 mg for children 30 days to 5 years.

Diazepam can be given by deep intramuscular injection if intravenous administration is not possible.

CAUTION: Be prepared to assist pulmonary ventilation mechanically if respiration is depressed, to intubate the trachea if laryngospasm occurs, and to counteract hypotensive reactions.

G. Hemodialysis has not proven to be effective in poisonings by phenolic substances. Forced diuresis is of little or no benefit in reducing body burden. There has been insufficient testing of hemoperfusion to establish its value in accelerating elimination of phenols.

4. **IF** nitrophenol or nitrocresol has been **INGESTED** in a quantity sufficient to cause poisoning, the stomach and intestine must be emptied and measures taken to limit absorption of residual toxicant. The effectiveness of induced emesis and gastric lavage in removing toxicant from the stomach diminishes rapidly with the passage of time.

A. **IF** ingestion occurred within the last few hours, and **IF** the patient is **FULLY ALERT**, give **SYRUP OF IPECAC**, followed by 1–2 glasses of water, to induce vomiting. The dosage of Syrup of Ipecac for adults and children over 12 years is 30 ml; the dosage for children under 12 years is 15 ml.

CAUTION: OBSERVE the patient closely **AFTER** administering **IPECAC**. Position the patient in left lateral decubitus, head below the level of the stomach. If consciousness level declines or if vomiting does not occur in 30 minutes, proceed immediately to **PROTECT THE AIRWAY**, then **INTUBATE**, **ASPIRATE**, and **LAVAGE** the stomach (see below).

B. **IF** the patient is **NOT FULLY ALERT** when first examined, proceed directly to **PROTECT THE AIRWAY**, insert a large bore orogastric tube, and empty to stomach by **ASPIRATION** and **LAVAGE** with a slurry of **ACTIVATED CHARCOAL.** See Chapter 1, TREATMENT, Section 6, p. 8.

C. Following emesis or lavage, administer **ACTIVATED CHARCOAL** and **CATHARTIC** by ingestion or by orogastric tube, as recommended in Chapter 1, TREATMENT, Section 6, page 8.

D. If several hours have elapsed since ingestion, and if the patient is fully alert, **ADMINISTER ACTIVATED CHARCOAL AND CATHARTIC ORALLY.**

E. **REPEATED** administration of **ACTIVATED CHARCOAL** at half or more the initial dosage every 2–4 hours may be beneficial.

CAUTION: Catharsis may lead to dehydration and electrolyte disturbances, particularly in children. Fluid balance and serum electrolytes should be monitored. There may be some advantage in giving repeated doses of cathartics to adults, but caution must be exercised in children. Administration of cathartic should stop when a charcoal stool appears.

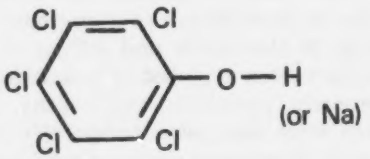
F. Save a sample of emesis or initial gastric washings for chemical analysis.

5. During convalescence, administer a high-calorie, high-vitamin diet to restore body fat and carbohydrate.
6. Discourage subsequent contact with the toxicant for 4–8 weeks (depending on severity of poisoning) to allow full restoration of normal metabolic processes.

CHAPTER 9

PENTACHLOROPHENOL

CHEMICAL STRUCTURE



COMMERCIAL PRODUCTS

PCP, Penta, Penchlorol, Santophen, Chlorophen, Pentacon, Penwar, Sinituho. The sodium salt is sodium pentachlorophenate.

In various products, pentachlorophenol has been used as an herbicide, algacide, defoliant, wood preservative, germicide, fungicide, and molluscicide. As a wood preservative, it is commonly applied as a 0.1% solution in mineral spirits, No. 2 fuel oil, or kerosene. It is used in pressure treatment of lumber at 5% concentration. Weed killers contain higher concentrations. PCP is no longer available for over-the-counter sale in the United States.

Pentachlorophenol volatilizes from treated wood and fabric. It is virtually odorless. Excessively treated interior surfaces may be a source of exposure sufficient to cause irritation of eyes, nose, and throat.

Technical PCP contains lower chlorinated phenols (4–12%) plus traces of chlorobenzodioxins, chlorobenzofurans, and chlorobenzenes.

TOXICOLOGY

PCP is efficiently absorbed across the skin, the lung, and the gastrointestinal lining. It is rapidly excreted, mainly in the urine as unchanged PCP and as PCP glucuronide. In the blood, a large fraction of absorbed PCP is protein-bound.

The residence half-life of PCP in humans is about 27–36 hours. Because minute amounts of PCP are consistently detectable in the blood and urine of the general population, a continuing low-level intake (micrograms per day) of PCP by virtually everyone is implied.

In adequate concentration, PCP is irritating to mucous membranes and skin. Contact dermatitis occurs commonly in workers having contact with PCP.

Internally, large doses are toxic to the liver, kidneys, and nervous system. An important mechanism of toxic action is increased cellular oxidative metabolism resulting from the uncoupling of oxidative phosphorylation. This leads to increased heat production (hyperthermia).

Severe poisoning and death have occurred as a result of intensive PCP exposure. Dermal absorption has been the basis of virtually all occupational poisonings. Most adult fatalities have occurred in persons working in hot environments where hyperthermia is poorly tolerated. Several infant deaths occurred in a nursery where a PCP-containing diaper rinse had been used. Chloracne has occurred in production workers, possibly due to chlorodioxin contaminants. Individual cases of exfoliative dermatitis of the hands and diffuse urticaria and angioedema of the hands have been reported in intensively exposed workers. Cases of aplastic anemia, peripheral neuropathy, and leukemia have been reported which were associated temporally with PCP exposure. Causal relationships in these cases were not established.

Albuminuria, glycosuria, aminoaciduria, and elevated BUN reflect renal injury. Liver enlargement, anemia and leukopenia have been reported in some intensively exposed workers. Elevated serum alkaline phosphatase, GOT, and LDH enzymes indicate significant insult to the liver, including both cellular damage and some degree of biliary obstruction.

SYMPTOMS AND SIGNS OF POISONING

IRRITATION of the nose, throat, and eyes is the most common effect of airborne PCP, causing stuffy nose, scratchy throat, and tearing. Dermal exposure may lead to contact dermatitis, or more rarely, diffuse urticaria or chloracne.

Commonly reported symptoms of systemic poisoning by PCP are profuse **SWEATING**, weakness, dizziness, anorexia, nausea, and—in workers exposed over long periods—weight loss. Indications of severe acute poisoning are **HYPERTHERMIA**, muscle spasms, tremor, labored breathing, a sense of constriction in the chest, abdominal pain and vomiting, restlessness, excitement, and mental confusion. Tachycardia and increased respiratory rate are usually apparent. Intense **THIRST** is characteristic.

CONFIRMATION OF POISONING

PCP can be measured in blood, urine, and adipose tissue by gas-liquid chromatography. Up to about 100 parts per billion may be found in the blood and urine of persons having no recognized exposure. Food is probably the main source of this microgram-level dosage. In addition to minute residues of synthetic PCP in food, water, and air, some PCP may derive from biotransformation of other chlorinated organic compounds.

Based on studies of persons occupationally exposed to PCP, manifestations of systemic toxicity probably do not appear in adults until blood and urine concentrations reach at least one part per million (0.1 mg%, or 1,000 parts per billion). PCP serum concentrations of 13 parts per million have been found in symptomatic occupationally exposed workers. Serum concentrations of 46 and 97 parts per million have been measured in fatal poisonings.

If poisoning is strongly suspected on the basis of exposure, symptoms, and signs, **DO NOT POSTPONE TREATMENT** until diagnosis is confirmed.

TREATMENT

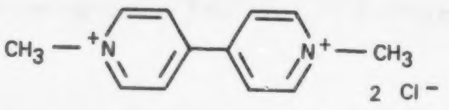
Treatment recommendations in poisonings by PCP are essentially the same as those for poisonings by **NITROPHENOLIC** and **NITROCRESOLIC HERBICIDES**, discussed in Chapter 8, page 70.

Exchange transfusion was used to rescue newborns inadvertently poisoned by PCP in a hospital.

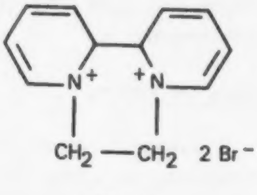
CHAPTER 10

PARAQUAT AND DIQUAT

CHEMICAL STRUCTURES



PARAQUAT



DIQUAT

Paraquat and diquat are identified chemically as **DIPYRIDYLS.**

COMMERCIAL PRODUCTS

Paraquat is a synthetic nonselective contact herbicide, usually marketed as the dichloride salt. Dimethyl sulfate salts are also produced. Liquid technical products range from 20% to 50% concentration. Names of liquid concentrates are: Ortho Paraquat CL, Ortho Paraquat Plus, Cekuquat, Crisquat, Herbaxon, Herboxone, Dextrone, Esgram, Gramocil, Gramoxone, Goldquat 276, Sweep, Osaquat Super, Gramonol, Toxer Total, Pillarxone, Pillarquat. Paraquat is commonly formulated in combination with other herbicides:

With diquat: Actor, Preeglone, Preglone, Priglone, Weedol (a 2.5% soluble granule formulation).

With monolinuron: Gramonol

With diuron: Gramuron, Para-col, Tota-col, Dexuron

With simazine: Terraklene, Pathclear

Diquat is usually prepared as the dibromide monohydrate salt, 20% to 25% in liquid concentrates. Deiquat and reglon are alternative common names. Commercial products are: Ortho Diquat, Aquacide, Dextrone, Reglone, Reglox, Weedtrine-D. Combinations with paraquat are listed above. Diquat is still used as a water herbicide, but is now applied as a dessicant and terrestrial herbicide as well.

TOXICOLOGY AND MANIFESTATIONS OF POISONING

Paraquat

Particularly in concentrated form, paraquat causes injury to tissues with which it comes into contact. It leaves the skin of the hands dry and fissured, sometimes resulting in loss of fingernails. Prolonged contact with skin may cause blistering and ulceration, with subsequent absorption of paraquat in sufficient dosage to cause systemic poisoning. Prolonged inhalation of spray droplets may cause nosebleed. Eye contamination results in severe conjunctivitis and sometimes protracted and even permanent corneal opacification. When ingested in adequate dosage (see below), paraquat has life-threatening effects on the gastrointestinal tract, kidney, liver, heart, and other organs. The first phase of systemic poisoning consists of swelling, edema, and ulceration of the mucosal linings of the mouth, pharynx, esophagus, stomach, and intestine. Centrizonal hepatocellular injury along with damage to the proximal renal tubules, myocardium, and skeletal muscle (sometimes including focal necrosis) are the main features of the second phase. The nervous system and pancreas are affected in some cases. The third phase—injury to the lung—usually becomes evident 2–14 days following ingestion, although, in some cases, pulmonary edema has developed only a few hours after paraquat has been swallowed. Paraquat is selectively concentrated in lung tissue where it destroys lung parenchymal cells probably by generation of free-radical oxygen and subsequent lipid peroxidation. Hemorrhage, edema fluid, and leukocytes infiltrate the alveolar spaces, after which there is rapid proliferation of fibroblasts. Severe impairment of gas exchange causes death from anoxemia and tissue anoxia. Remarkably, essentially full recovery of pulmonary function occurs following paraquat poisonings which are survived. Although absorption across intact skin is slow, abraded or eroded skin allows efficient absorption. Fatal poisonings are reported to have occurred as a result of protracted dermal contamination by paraquat.

The effect of paraquat on renal tubule cells is more likely to be reversible than the effect on lung tissue, but impaired renal function may play a critical role in determining the outcome of paraquat poisoning. Normal tubule cells actively secrete paraquat into the urine, clearing it efficiently from the blood. However, high blood concentrations poison the secretory mechanism and may destroy the cells. Because the kidney is almost the exclusive route of paraquat elimination from body tissues, renal failure fosters a build-up of tissue concentrations, including those in the lung. Unfortunately, this pathogenetic sequence may occur in the first several hours following paraquat ingestion, generating lethal concentrations of paraquat in lung tissue before therapeutic measures to limit absorption and enhance disposition have taken effect. It is probably for this reason that methods for enhancing paraquat disposition several hours following ingestion have had little influence on mortality.

The hepatic injury from paraquat may be severe enough to cause jaundice, but hepatotoxicity is rarely a major determinant of clinical outcome. Elevated alkaline phosphatase, AST, ALT, and LDH are indications of hepatocellular insult; jaundice signifies more severe injury.

Early symptoms and signs of poisoning by ingested paraquat are burning pain in the mouth, throat, chest, and upper abdomen, due to the corrosive effect of paraquat on the mucosal lining. Giddiness, headache, fever, myalgia, and diarrhea (sometimes bloody) occur. Pancreatitis may cause severe abdominal pain. Proteinuria, hematuria, pyuria, and azotemia reflect renal injury. Oliguria/anuria indicate acute tubular necrosis.

Progressive declines in arterial oxygen tension and CO diffusion capacity commonly precede pulmonary symptomatology. Cough, dyspnea, and tachypnea usually appear 2–4 days following paraquat ingestion, but may be delayed as long as 14 days. Progressive cyanosis and air hunger reflect deteriorating gas exchange in the damaged lung. Coma usually precedes death. In some cases, the coughing up of frothy sputum (pulmonary edema) is the early and principal manifestation of paraquat lung injury.

Clinical experience has offered a rough dose-effect scale on which to base prognosis in cases of paraquat ingestion (J. A. Vale, et al., Human Toxicology, 6:41–47, 1987):

I. Less than 20 mg paraquat ion per kg body weight (less than 7.5 ml of 20% (w/v) paraquat concentrate). No symptoms, or only gastrointestinal symptoms occur. Recovery is likely.

II. Twenty to 40 mg paraquat ion per kg body weight (7.5–15.0 ml of 20% (w/v) paraquat concentrate). Gastrointestinal, renal, hepatic and pulmonary damage by paraquat occurs. Pulmonary fibroplasia ensues. Death occurs in most cases, but may be delayed 2–3 weeks.

III. More than 40 mg paraquat ion per kg body weight (more than 15.0 ml of 20% (w/v) paraquat concentrate). Multiple organ damage occurs as in class II, but is more rapidly progressive. Often characterized by marked ulceration of the oropharynx. Mortality is essentially 100% in 1 to 7 days.

Although much concern has been expressed about effects of smoking paraquat-contaminated marijuana, toxic effects by this mechanism have been either very rare or nonexistent. Most paraquat that contaminates marijuana is pyrolyzed during smoking to dipyridyl. Dipyridyl is a product of combustion of leaf material itself (including marijuana) and presents little toxic hazard.

It is tragic that use of paraquat as a suicidal agent has increased in recent years, particularly in Japan and also in developing countries. Several strategies are being tested to reduce the frequency of these occurrences: addition of emetics, stenching agents, gelling substances.

Diquat

Diquat is somewhat less damaging to skin than paraquat, but irritant effects may appear following dermal contamination with the concentrate. There is probably significant absorption of diquat across abraded or ulcerated skin.

Systemically absorbed diquat is not selectively concentrated in lung tissue, as is paraquat, and pulmonary injury by diquat is less prominent. However, diquat has severe toxic effects on the central nervous system that are not typical of paraquat poisoning although brain injury has been observed post-mortem in some fatal paraquat poisonings. Renal damage is an important feature of poisonings by both agents. The kidney is the principal excretory pathway for diquat absorbed into the body.

Early symptoms of poisoning by ingested diquat are similar to those from paraquat, reflecting its corrosive effect on tissues: burning pain in the mouth, throat, chest, and abdomen. Intense nausea, vomiting, and diarrhea are characteristic. If the dosage was small, these symptoms may be delayed 1-2 days. Blood may appear in the vomitus and feces. Intestinal ileus, with pooling of fluid in the gut, has characterized several human poisonings by diquat. Dehydration, hypotension, and tachycardia may result and shock is a common cause of death. Agitation, restlessness, disorientation, and psychotic behavior have been early manifestations of some diquat poisonings. Tonic-clonic seizures and coma may supervene. Proteinuria, hematuria, and pyuria may progress to renal failure and azotemia. Elevations of serum alkaline phosphatase, AST, ALT, and LDH reflect liver injury. Jaundice may develop. If the patient survives several hours or days, circulatory function may fail due to toxic myocardiopathy, or bronchopneumonia may develop.

Over the past decade, the great majority of poisonings by paraquat and diquat have been caused by ingestion—with suicidal intent in most cases. Nearly all of the few poisonings caused by occupational exposure have been survived, but the mortality rate among persons who have swallowed paraquat or diquat remains distressingly high (60%). Avoidance of this mortality will probably have to rely on preventive strategies or on stopping gastrointestinal absorption very soon after the toxicant has been ingested. Even though intestinal absorption of dipyridyls is relatively slow, lethal uptake by critical organs and tissues apparently occurs within 18 hours, possibly within 6 hours, following ingestion of toxic quantities of paraquat or diquat. Dipyridyls have large volumes of distribution. Once distribution to tissues has occurred, measures to remove dipyridyls from the blood are very inefficient in reducing the total body burden.

CONFIRMATION OF ABSORPTION

At some treatment facilities, a simple colorimetric test is used to identify paraquat and diquat in the urine, and give a rough indication of the magnitude of absorbed dose. To one volume of urine is added 0.5 volume of freshly prepared 1% sodium dithionite (sodium hydrosulfite) in one normal sodium hydroxide. Observe color at end of one minute. Development of a blue color indicates the presence of paraquat in excess of 0.5 mg per liter. **Both positive and negative controls must be run to insure that the dithionite has not undergone oxidation in storage.**

When urine collected within 24 hours of paraquat ingestion is tested, the dithionite test appears to have some approximate prognostic value: concentrations less than one milligram per liter (no color to light blue) generally predict survival, while concentrations in excess of one milligram per liter (navy blue to dark blue) often foretell a fatal outcome.

Diquat in urine yields a green color. There is less experience with the dithionite test in diquat poisonings; however, the association of bad prognosis with intense color is probably similar.

Paraquat and diquat can be measured in blood and urine by spectrophotometric, gas chromatographic, liquid chromatographic, and radioimmunoassay methods. These are available in localities where the frequency of paraquat poisonings (chiefly suicides) has stimulated research aimed at more effective therapy. Paraquat poisonings in which plasma concentrations do not exceed 2.0, 0.6, 0.3, 0.16, or 0.1 mg per liter at 4, 6, 10, 16, and 24 hours, respectively, after ingestion are likely to survive (Proudfoot, A.T. et al. The Lancet II:330–332, 1979).

TREATMENT

1. Contaminated **SKIN** must be **FLUSHED** immediatley with copious amounts of water. Material splashed in the **EYES** must be removed by **PROLONGED IRRIGATION** with clean water. Eye contamination should thereafter be treated by an ophthalmologist. Mild skin reactions usually respond to simple avoidance of further contact, but the irritation may take several weeks to resolve. Severe injuries, with inflammation, cracking, secondary infection, or nail injury should be treated by a dermatologist.
2. If paraquat or diquat have been ingested in any amount, **IMMEDIATE ADMINISTRATION OF ADSORBENT** is the one therapeutic measure most likely to affect the outcome of paraquat or diquat ingestion favorably. **BENTONITE** (7.5% suspension) and **FULLER'S EARTH** (30% suspension) are highly effective, but sometimes not available.

   Dosage of **BENTONITE AND FULLER'S EARTH:**

   Adults and children over 12 years: 100–150 gm.

   Children under 12 years: 2 gm/kg body weight.

   CAUTION: Hypercalcemia and fecaliths have sometimes occurred following administration of fuller's earth.

   ACTIVATED CHARCOAL is nearly as effective, and is generally available. Give as much of a 30 gm per 240 ml suspension as the patient will swallow. Encourage the victim to swallow the adsorbent even though spontaneous vomiting continues. Then, after taking precautions to protect the airway (see Chapter 1, TREATMENT, Section 6, p. 8), carefully intubate the stomach and lavage repeatedly with a slurry of adsorbent. Instill the suspension of adsorbent as fast as the gut accepts it. Repeated administration of charcoal or other absorbent every 2-4 hours may be beneficial. Include **SORBITOL** in the first dose of adsorbent suspension. Dosage of **SORBITOL:**

Adults and children over 12 years: 1-2 gm/kg body weight to a maximum of 150 gm.

Children under 12 years: 1.0-1.5 gm/kg body weight to a maximum of 50 gm.

Seventy percent sorbitol should be diluted half-and-half with water before administration.

Prompt administration of adsorbent and thorough flushing of the gut are the measures which offer the best opportunity for survival.

CAUTION: Because corrosive damage to the esophagus and stomach may render these structures vulnerable to perforation, the gastric lavage tube must be introduced very gently.

CHECK FREQUENTLY FOR BOWEL SOUNDS. Ileus occurs commonly in diquat poisoning, less often in paraquat poisoning. Cathartics should not be administered if the gut is atonic; instillation of fluid by stomach tube should be slowed or stopped if ileus is present.

3. Secure a blood sample as soon as possible for paraquat analysis.
4. **DO NOT ADMINISTER SUPPLEMENTAL OXYGEN.** High concentrations of oxygen in the lung increase the injury induced by paraquat, and possibly by diquat as well. There may be some advantage in placing the patient in a moderately hypoxic environment, i.e., 15%-16% oxygen, although the benefit of this treatment measure has not been established empirically in human poisonings. When the lung injury is so far advanced that there is no expectation of recovery, oxygen may be given to relieve air hunger.
5. Administer **INTRAVENOUS FLUIDS:** isotonic saline, Ringer's solution, and 5% glucose in water. This is highly advantageous early in poisonings as a means of correcting dehydration, accelerating toxicant excretion, reducing tubular fluid concentrations of paraquat, and correcting metabolic acidosis, when this occurs. However, fluid balance must be monitored carefully to forestall fluid overload if renal failure develops. Monitor the urine regularly for protein and cells, to warn of impending tubular necrosis. Intravenous infusions must be stopped if failure occurs, and **EXTRACORPOREAL HEMODIALYSIS** must be instituted to maintain normal extracellular fluid composition. Hemodialysis is not effective in clearing paraquat or diquat from the blood and tissues.
6. **HEMOPERFUSION** over cellophane-coated activated charcoal may be considered. The procedure has been used in many para-

quat poisonings because the adsorbent does efficiently remove paraquat from the perfused blood. However, recent reviews of effectiveness have failed to show any reduction in mortality as a result of hemoperfusion. The apparent reason for this is the very small proportion of paraquat body burden carried in the circulating blood even when only a few hours have elapsed after ingestion. Theoretically, a patient who can be hemoperfused within 10 hours of paraquat ingestion may derive some marginal benefit, but this has not been demonstrated.

If hemoperfusion is attempted, blood calcium and platelet concentrations must be monitored. Calcium and platelets must be replenished if these constituents are depleted by the procedure.

7. **CONVULSIONS** and psychotic behavior sometimes encountered in diquat poisoning may be best controlled by **DIAZEPAM**, given slowly intravenously.

   Dosage of **DIAZEPAM:**

   Adults and children over 12 years: 5–10 mg. Repeat every 10–15 minutes, if necessary, to a maximum of 30 mg.

   Children 5 to 12 years: 0.25–0.40 mg/kg body weight. Repeat every 15 minutes if necessary, to a maximum of 10 mg.

   Children under 5 years: 0.25–0.40 mg/kg body weight. Repeat every 15 minutes if necessary, to a maximum of 5 mg.

8. Many drugs have been tested in animals or given in human dipyridyl poisonings without clear evidence of benefit or harm: corticosteroids, superoxide dismutase, propranolol, cyclophosphamide, vitamin E, riboflavin, niacin, ascorbic acid, clofibrate, desferrioxamine, acetylcysteine, and terpin hydrate.
9. Morphine sulfate is usually required to control the pain associated with deep mucosal erosions of the mouth, pharynx, and esophagus, as well as abdominal pain from pancreatitis and enteritis. Dosage for adults and children over 12 years: 10–15 mg subcutaneously every 4 hours. Dosage for children under 12 years: 0.1–0.2 mg/kg body weight every 4 hours.
10. Mouthwashes, cold fluids, ice cream, or anesthetic lozenges may help to relieve pain in the mouth and throat.

CHAPTER 11

OTHER HERBICIDES

Many herbicides are now available for use in agriculture and for lawn and garden weed control. This chapter discusses herbicides other than the chlorophenoxys, nitro- and chloro-phenols, arsenicals, and dipyridyls, which are subjects of separate chapters. Many modern herbicides kill weeds selectively by impairing metabolic processes that are unique to plant life. For this reason, their systemic toxicities in mammals are generally low. Nonetheless, there are some which pose a significant risk of poisoning if handled carelessly, and many are irritating to eyes, skin, and mucous membranes.

For several good reasons, all of the herbicides mentioned in this chapter should be handled and applied only with full attention to hygienic measures that minimize personal contact. Many formulations contain adjuvants (stabilizers, penetrants, safeners, surfactants) that may have significant irritating and toxic effects. A number of premixed formulations contain two or more active ingredients; the companion pesticides may be more toxic than the principal herbicide. Finally, some individuals exhibit unique sensitivities to chemicals that are not predictable on the basis of past human exposure experience. Good hygienic practice should, therefore, not be disregarded because a pesticide is reported to have a high LD_{50} in laboratory rodents, or is said to be "harmless to humans." The rodent LD_{50} rating is based solely on lethality; it says nothing of dosage necessary to produce symptoms or signs, or cause injury or disease after long latency, subclinical biochemical effects, or other nonlethal effects on health.

The fate of these compounds after they have been absorbed by humans should be understood by health professionals who may need to assess the consequences of prior exposure. The water-soluble herbicides are not retained in body tissues for long periods, as were the old lipophilic organochlorine insecticides, such as DDT. Some undergo biotransformation in the body, others do not. Most are excreted, mainly in the urine, within one to four days.

The following table is a synoptic listing of the more commonly used herbicides other than those discussed in separate chapters. The rat acute oral LD_{50} is given as a rough index of potential lethal toxicity. (If several values are reported by various sources, the lowest is recorded here.) The adverse effect information given is drawn from many sources, including product labels, textbooks, published case histories, and some unpublished reports. The listing cannot be considered inclusive, either of herbicide products or of effects.

Chemical Class	Generic Name	Proprietary Names	Acute Oral LD_{50}[1] mg/kg	Known or Suspected Adverse Effects
Acetamides	allidochlor	Randox, CDAA	750	Irritating to eyes and skin.
	metolachlor	Dual, Bicep, Primagram, Pennant, Primextra, Codal	2,780	
Anilides	alachlor	Lasso, Lazo, Alanox	1,800	Mild irritant.
	propachlor	Ramrod, Bexton	710	Dermal irritant and sensitizer.
	propanil	DPA, Erban, Chem Rice, Propanex, Riselect, Stam, Stampede, Supernox, Surpur	1,384	Irritating to skin, eyes, and respiratory tract.
Aliphatic acids	trichloroacetic acid	TCA, NaTA, Varitox	5,000	Irritating to skin, eyes, and respiratory tract.
	dichloropropionic acid, dalapon	Dalapon, Basfapon, Dowpon, Ded-Weed, Revenge	970	
Benzamide	pronamide	Kerb	8,350	Moderately irritating to eyes.
Benzoic, anisic acid derivatives	trichlorobenzoic acid	TCBA, Benzac, Tribac, 2, 3, 6-TBA	750	Moderately irritating to skin and respiratory tract.
	chloramben	Amiben	3,500	
	dicamba	Banvel	1,700	
Benzonitriles	dichlobenil	Casoron, Decabane, Dyclomec, Barrier	3,160	Minimal toxic, irritant effects.
Benzothiadiazinone dioxide	bentazon	Basagran	2,063	Irritating to eyes and respiratory tract.
Carbamates and thiocarbamates (herbicidal)	asulam	Asulox	5,000	Some are irritating to eyes, skin, and respiratory tract, particularly in concentrated form. Some may be weak inhibitors of cholinesterases.
	terbucarb	Azac, Azar	>34,000	
	butylate	Sutan	3,500	
	cycloate	Ro-Neet	2,000	
	pebulate	Tillam, PEBC	921	
	vernolate	Surpass	1,800	
	EPTC	Eptam, Eradicane	1,630	
	diallate	Avadex, Pyradex	395	
	triallate	Avadex BW	1,675	
	thiobencarb	Bolero, Saturn	1,300	
Carbanilates	barban	Carbyne	1,350	Irritant and sensitizer. May generate methemoglobin at high dosage. Weak cholinesterase inhibitor.
	chlorpropham	Furloe, Bud-Nip, Sprout-Nip, Beet-Kleen, Chloro-IPC, Unicrop-CIPC	3,800	Skin irritants. May generate methemoglobin at high dosage.

—Continued

Chemical Class	Generic Name	Proprietary Names	Acute Oral LD$_{50}$[1] mg/kg	Known or Suspected Adverse Effects
Chloropyridinyl	triclopyr	Garlon, Crossbow Turflon	630	Irritant to skin and eyes.
Cyclohexenone derivative	sethoxydim	Poast	3,125	Irritating to skin and eyes.
Dinitroaminobenzene derivatives	butralin	Amex, Tamex	12,600	May be moderately irritating. These herbicides do not uncouple oxidative phosphorylation or generate methemoglobin.
	isopropalin	Paarlan	>5,000	
	pendimethalin	Prowl, Stomp, Accotab, Herbadox, Go-Go-San, Wax Up	1,250	
	oryzalin	Surflan, Dirimal	>10,000	
Fluorodinitrotoluidine compounds	benfluralin	Benefin, Balan, Balfin, Quilan	>10,000	May be mildly irritating. These herbicides do not uncouple oxidative phosphorylation or generate methemoglobin.
	dinitramine	Cobex	3,000	
	ethalfluralin	Sonalan	>10,000	
	fluchloralin	Basalin	1,550	
	profluralin	Tolban	1,808	
	trifluralin	Treflan, TR-10	>10,000	
Isoxazolidinone		Command	1,369	May be moderately irritating.
Nicotinic acid-isopropylamine derivative		Arsenal	>5,000	Irritating to eyes and skin. Does not contain arsenic.
Oxadiazolinone	oxadiazon	Ronstar	>3,500	Minimal toxic and irritant effects.
Phosphonates	glyphosate	Roundup, Glifonox	4,300	Minimal toxic and irritant properties.
	fosamine ammonium	Krenite	24,000	Irritating to eyes, skin, and upper respiratory tract.
Phthalates	chlorthal-dimethyl	Dacthal, DCPA	>10,000	Moderately irritating to eyes.
	endothall	Aquathol	51	Free acid is highly toxic. Irritating to skin, eyes, and respiratory tract. See Chapter 15, page 153.
Picolinic acid compound	picloram	Tordon, Grazon	8,200	Irritating to skin, eyes, and respiratory tract. Low systemic toxicity.
Triazines	ametryn	Ametrex, Evik, Gesapax	1,750	
	atraton	Atratone, Gestamin	1,465	

—Continued

Chemical Class	Generic Name	Proprietary Names	Acute Oral LD_{50}[1] mg/kg	Known or Suspected Adverse Effects
	atrazine	AAtrex, Atranex, Crisazina, Griffex, Vectal SC	1,780	Systemic toxicity is unlikely unless large amounts have been ingested. Some triazines are moderately irritating to the eyes, skin, and respiratory tract.
	cyanazine	Bladex, Fortrol	288	
	desmetryn	Semeron	1,390	
	isomethiozin	Tantizon	>10,000	
	metribuzin	Sencor, Lexone, Sencoral, Sencorex	1,100	
	prometryn	Caparol, Gesagard, Primatol Q, Prometrex	5,235	
	propazine	Gesamil, Milogard, Milo-Pro, Primatol P	>5,000	
	simazine	Aquazine, Cekusan Gesatop, Primatol S, Princep, Caliber 90	>5,000	
	terbuthylazine	Gardoprim, Primatol M	2,000	
	terbutryn	Igran, Prebane, Terbutrex	2,500	
	prometon	Gesafram 50, Ontracic 800,	2,276	
		Pramitol 25E		This particular formulation of prometon is strongly irritating to eyes, skin, and respiratory tract.
Triazole	amitrole, aminotriazole	Amerol, AT-90, Amitrol-T, Azolan, Azole, Cytrol, Diurol, Herbizole, Simazol, Weedazol	24,600	Minimal systemic toxicity. Slight irritant effect.
Uracils	bromacil	Borea, Bromax, Hyvar, Rout, Uragan, Urox B	5,200	Irritant to skin, eyes, and respiratory tract.
	lenacil	Ban-Hoe, Venzar	>11,000	Moderately irritating.
	terbacil	Sinbar	>5,000	
Urea derivatives	chlorimuron ethyl	Classic	>4,000	Systemic toxicity is unlikely unless
	chlorotoluron	D[illegible]an, Tolurex	>10,000	
	chloroxuron	Tenoran	3,700	
	difenoxuron	Lironion	>7,750	
	diuron	Cekiuron, Crisuron, Dailon,	3,400	

—Continued

Chemical Class	Generic Name	Proprietary Names	Acute Oral LD_{50}[1] mg/kg	Known or Suspected Adverse Effects
		Diater, Di-on, Direx, Diurex, Diurol, Diuron, Karmex, Rout, Unidron, Vonduron		large amounts have been ingested. Many substituted ureas are irritating to eyes, skin, and mucous membranes.
	fluometuron	Cotoran, Cottonex	8,900	
	isoproturon	Alon, Arelon, Belgran, Graminon, IP50, Tolkan	1,826	
	linuron	Afalon, Linex 4L, Linorox, Linurex, Lorox, Sarclex	1,500	
	methabenz-thiazuron	Tribunil	>2,500	
	metobromuron	Patoran, Pattonex	2,603	
	metoxuron	Deftor, Dosanex, Dosaflo, Purivel, Sulerex	3,200	
	monolinuron	Aresin, Afesin, Arresin	2,100	
	monuron	Monuron	3,600	
	neburon	Granurex, Neburex Herbalt	>11,000	
	siduron	Tupersan	>7,500	
	sulfometuron methyl	Oust	>5,000	
	tebuthiuron	Spike, Graslan	644	
	tetrafluoron	Tomilon	1,265	

CONFIRMATION OF TOXICANT ABSORPTION

Although there are analytical methods for residues of many of the herbicides mentioned in this chapter, and for some of the mammalian metabolites generated from them, these procedures are not generally available to confirm human absorption of the chemicals. Prior exposure must be determined from a recent history of occupational contact or accidental or deliberate ingestion.

TREATMENT OF TOXICOSIS

1. Skin contamination should be removed promptly by washing with soap and water. Contamination of the eyes should be treated immediately by prolonged flushing of the eyes with copious amounts of clean water. If dermal or ocular irritation persists, medical attention should be obtained without delay.

2. **INGESTIONS** of these herbicides are likely to be followed by vomiting and diarrhea due to the irritant properties of most of the toxicants. Management depends on: 1) the best estimate of quantity originally ingested, 2) time elapsed since ingestion, 3) effectiveness of vomiting, and 4) the clinical status of the subject. **ACTIVATED CHARCOAL** is probably effective in limiting irritant effects and reducing absorption of most or all of these herbicides. Aluminum hydroxide gels may be useful in neutralizing the irritant actions of the more acidic agents. Sorbitol should be given to induce catharsis if bowel sounds are present and if spontaneous diarrhea has not already commenced. Dehydration and electrolyte disturbances may be severe enough to require oral or intravenous fluids.

   There are no specific antidotes for poisoning by these herbicides. In the case of suicidal ingestions, particularly, the possibility must always be kept in mind that multiple toxic substances may have been swallowed.

   A. If large amounts of herbicide have been ingested, and if the patient is fully alert, induce **EMESIS** with Syrup of Ipecac, followed by several glasses of water. Dosage for adults and children over 12 years: 30 ml; dosage for children under 12 years: 15 ml. When vomiting has stopped, give **ACTIVATED CHARCOAL.** Add **SORBITOL** to the charcoal slurry unless diarrhea has already commenced. If, for some reason, the patient is not fully alert, put in place a cuffed endotracheal tube to protect the airway, then aspirate and lavage the stomach with a slurry of activated charcoal. Leave a quantity of charcoal, with sorbitol, in the stomach before withdrawing the stomach tube (see Chapter 1, TREATMENT, Section 6, page 8). Repeated administration of charcoal at half or more the initial dosage every 2–4 hours may be beneficial.

   B. If the amount of ingested herbicides was small, if effective emesis has already occurred, or if treatment is delayed, administer the activated charcoal and sorbitol by mouth.

   C. If serious dehydration and electrolyte depletion have occurred as a result of vomiting and diarrhea, monitor blood electrolytes and fluid balance and administer intravenous infusions of glucose, normal saline, Ringer's solution, or Ringer's-lactate to restore extracellular fluid volume and electrolytes. Follow this with oral nutrients as soon as fluids can be retained. Fluids serve to support excretion of the toxicants.

   D. Supportive measures are ordinarily sufficient for successful management of excessive exposures to these herbicides (endothall is an exception—see Chapter 15, p. 154). If the patient's condition deteriorates in spite of good supportive care, the operation of an alternative or additional toxicant should be suspected.

CHAPTER 12

FUNGICIDES

Fungicides are extensively used in industry, agriculture, the home, and garden for: 1) protection of seed grain during storage, shipment and germination; 2) protection of mature crops, berries, seedlings, flowers, and grasses in the field, in storage, and during shipment; 3) suppression of mildews that attack painted surfaces; 4) control of slime in paper pulps; and 5) protection of carpet and fabrics in the home.

Fungicides vary enormously in their potential for causing adverse effects in humans. Historically, some of the most tragic epidemics of pesticide poisoning occurred because of mistaken consumption of seed grain treated with organic mercury or hexachlorobenzene. However, most fungicides currently in use are unlikely to cause frequent or severe systemic poisonings for several reasons: 1) many have low inherent toxicity in mammals and are inefficiently absorbed; 2) many are formulated as suspensions of wettable powders or granules, from which rapid, efficient absorption is unlikely; and 3) methods of application are such that relatively few individuals are intensively exposed. Apart from systemic poisonings, fungicides as a class have probably caused disproportionate numbers of irritant injuries to skin and mucous membranes, as well as some dermal sensitizations.

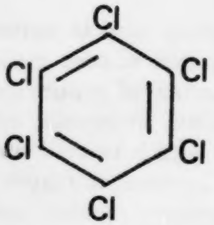
The following discussion considers the recognized adverse effects of widely used fungicides. In the case of those agents which have caused systemic poisoning, some recommendations for management of poisonings and injuries are set forth. For those fungicides not known to have caused systemic poisonings in the past, only general guidelines can be offered.

The discussion of fungicide-related adverse effects proceeds in this order:

- Substituted Benzenes
- Thiocarbamates
- Ethylene Bis Dithiocarbamates
- Thiophthalimides
- Copper Compounds
- Organomercury Compounds
- Organotin Compounds
- Cadmium Compounds
- Miscellaneous Organic Fungicides

SUBSTITUTED BENZENES

HEXACHLOROBENZENE (HCB, Anticarie, Ceku C.B., No Bunt).



Principal formulations are dusts and powders.

Hexachlorobenzene differs chemically and toxicologically from hexachlorocyclohexane, the gamma isomer of which (lindane) is still a widely used insecticide (see Chapter 3, TOXICOLOGY).

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY HEXACHLOROBENZENE

Although this seed protectant fungicide has only slight irritant effects and relatively low single-dose toxicity, long-term ingestion of HCB-treated grain by Turkish farm dwellers in the late 1950's caused several thousand cases of hepatic porphyria (porphyria cutanea tarda). This condition was due to impaired hemoglobin synthesis, leading to toxic end-products (porphyrins) in body tissues. The disease was characterized by excretion of red-tinged (porphyrin-containing) urine, bullous lesions of light-exposed skin, scarring and atrophy of skin with overgrowth of hair, liver enlargement, loss of appetite, arthritic disease, and wasting of skeletal muscle mass. Although most adults ultimately recovered after they stopped consuming the HCB-treated grain, some infants nursed by affected mothers died.

Hexachlorobenzene is effectively dechlorinated and oxidized in humans; trichlorophenols are the major urinary excretion products. Disposition is sufficiently prompt that occupationally exposed workers usually show only slight elevation of blood HCB concentrations. HCB is sometimes present in blood specimens from "non-occupationally exposed" persons up to concentrations of about 5 mcg per liter. Residue in food is the probable source.

CONFIRMATION OF POISONING BY HEXACHLOROBENZENE

HCB can be measured in blood by gas chromatography. Chlorophenol metabolites can be measured in the urine.

Although inherited disease and a number of exogenous agents may cause porphyrins to appear in the urine, a test for porphyrins may be useful for toxicologic diagnosis if there has been a known exposure to HCB or if a patient exhibits signs suggestive of porphyria cutanea tarda.

More than 0.5 mg per liter of porphyrins causes the untreated urine to exhibit a wine-red color in ordinary light. Somewhat lower concentrations can be detected by examining the urine in ultraviolet light (366 nm emission). Red or orange-red fluorescence indicates presence of uroporphyrins. However, background fluorescence from other urine constituents may mask this emission. If the above examination is negative, therefore, the following screening test for uroporphyrins can be performed:

1. Acidify the urine to pH 4.0 with acetic acid.
2. Heat for 15 minutes in a 100° C water bath.
3. Cool. Clean the outside of the test tube carefully, and examine for orange-red fluorescence in UV light (366 nm).

Urinary coproporphyrin excretion is also increased in HCB intoxication. The following test can be done to detect elevated concentrations:

1. Put 5 ml of clear (filtered) urine in a 16 x 150 mm quartz test tube.
2. Add in this order: 1 ml glacial acetic acid, 5 ml ethyl ether, then 3 drops fresh 3% hydrogen peroxide.
3. Close tube with a clean rubber stopper and invert 12 times to mix and extract. Allow to stand 10 minutes. (Centrifuge if necessary to break emulsion.)
4. Examine the ether layer in UV light for pink, violet, or rose red emitted light, indicating presence of coproporphyrins.

TREATMENT OF HEXACHLOROBENZENE TOXICOSIS

1. Dermal contamination should be washed off with soap and water. Contamination of the eyes should be removed by flushing with copious amounts of water. If irritation persists, specialized medical care should be obtained.
2. If a large amount of HCB has been ingested in the last few hours, and if copious vomiting has not already occurred, the stomach must be emptied and steps taken to limit gastrointestinal absorption. If the patient is fully alert and nervous system depression is not anticipated, oral administration of Syrup of Ipecac is probably the best way to empty the stomach.

   Dosage of SYRUP OF IPECAC:

   Adults and children over 12 years: 30 ml, followed by 2–3 glasses of water.

   Children under 12 years: 15 ml, followed by 1–2 glasses of water. Children less than one year should receive only 10–15 ml and should be under direct medical supervision if at all possible.

When vomiting stops after induced emesis, give charcoal and cathartic orally by adding sorbitol to the charcoal slurry.

Dosage of ACTIVATED CHARCOAL:

Adults and children over 12 years: 50–100 gm in 300–800 ml water.

Children under 12 years: 15–30 gm in 100–300 ml water.

Dosage of SORBITOL:

Adults and children over 12 years: 1–2 gm/kg body weight to a maximum of 150 gm per dose.

Children under 12 years: 1.0–1.5 gm/kg body weight to a maximum of 50 gm per dose.

If sorbitol is given separately, it should be diluted with an equal volume of water before administration.

If there are any indications of central nervous system depression, or if the patient fails to vomit within 30 minutes of Syrup of Ipecac administration, measures should be taken to protect the respiratory tract from aspiration of gastric contents (preferably a cuffed endotracheal tube), then the stomach should be emptied by gastric intubation, aspiration and lavage with a slurry of activated charcoal (see Chapter 1, TREATMENT, Section 6, page 8). Instill activated charcoal following lavage. Unless diarrhea has already commenced, include a cathartic (see above for dosage) to hasten elimination.

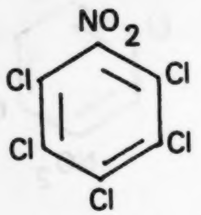
CAUTION: Do not instill fluid so rapidly that overloading of the stomach leads to vomiting or regurgitation, followed by aspiration. Serious electrolyte disturbances may follow catharsis, especially in young children. Monitor fluid balance and serum electrolytes.

If the amount of ingested HCB was small, or if treatment has been delayed several hours, or if spontaneous vomiting has effectively emptied the stomach, oral administration of charcoal and sorbitol at the doses recommended above probably represents optimal management.

If contact with the toxicant has been minimal (for example, oral contamination only, promptly flushed out of the mouth) administration of charcoal without a cathartic, followed by careful observation of the patient, probably represents optimal management.

3. In persons who have experienced significant tissue storage of HCB (as from protracted uptake of small quantities) administration of cholestyramine accelerates elimination by interrupting enterohepatic recirculation. It is usually administered in 3–8 gm doses, 4 times a day, before meals and at bedtime. Dose should be mixed with a pulpy fruit or liquid.
4. Persons affected by porphyria should avoid sunlight, which exacerbates the dermal injury by porphyrins.

PENTACHLORONITROBENZENE (PCNB, quintozene, Terraclor, Avicol, Botrilex, Earthcide, Folosan, Kobu, Kobutol, Pentagen, Tilcarex, Tri-PCNB).



This fungicide is used to dress seed and treat soil. Formulations include emulsifiable concentrates, wettable powders, and granules. Hexachlorobenzene is a minor contaminant of technical PCNB.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY PENTACHLORONITROBENZENE

High concentrations in prolonged contact with skin have caused sensitization in some tested volunteers, but neither irritation nor sensitization has been reported in occupationally exposed workers. One case of conjunctivitis and keratitis occurred following eye contamination. This resolved slowly but completely.

Systemic poisonings have not been reported. Disposition in laboratory animals is slow, probably due to enterohepatic recirculation. Excretion is chiefly biliary, with some conversion to pentachloroaniline, pentachlorophenol, and other metabolites in the liver. Although a methemoglobinemic effect might be suspected (as from nitrobenzene), this has not been reported in man or animals, nor has hepatic porphyria (as from hexachlorobenzene) been reported.

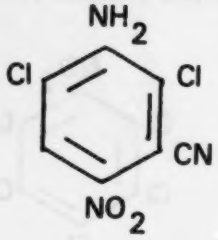
CONFIRMATION OF ABSORPTION OF PENTACHLORONITROBENZENE

PCNB and metabolites can be measured in body fluids by gas chromatography. The analysis is not widely available.

TREATMENT OF PENTACHLORONITROBENZENE TOXICOSIS

See HEXACHLOROBENZENE, TREATMENT OF TOXICOSIS, Sections 1, 2, and 3 above.

DICHLORAN (DCNA, ditranil, Botran, Allisan, Kiwi Lustr 277, Resisan).



Dichloran is formulated as wettable powder, dusts, and flowable powders.

TOXICOLOGY AND MANIFESTIONS OF POISONING BY DICHLORAN

This broad spectrum fungicide is widely used to protect perishable produce. It is absorbed by occupationally exposed workers, but promptly eliminated, at least partly in the urine. Residence half-life in man is probably less than 27 hours. Biotransformation products include dichloroaminophenol, which is an uncoupler of oxidative phosphorylation (enhances heat production). Extraordinary doses of dichloran given to laboratory animals cause liver injury and corneal opacities.

Based on laboratory animal studies and effects of similar compounds, large doses might be expected to cause liver injury, pyrexia, corneal opacities, and possibly methemoglobinemia. None of these have been observed in humans exposed to DCNA. Daily oral dosage of 10 mg per day for 90 days was tolerated by 20 adult male subjects without observable effect.

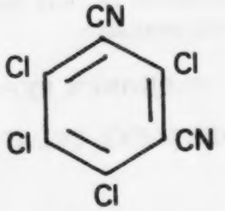
CONFIRMATION OF ABSORPTION OF DICHLORAN

Methods have been described for analysis of dichloran, but they are not widely available.

MANAGEMENT OF DICHLORAN EXPOSURE

See HEXACHLOROBENZENE, TREATMENT OF TOXICOSIS, Sections 1, 2, and 3 above.

CHLOROTHALONIL (Bravo, ClortoCaffaro, Clortosip, Daconil 2787, Exotherm Termil, Tuffcide).



Chorothalonil is available as wettable powder, water dispersible granules, and flowable powders.

Chlorothalonil has caused irritation of skin and mucous membranes of the eye and respiratory tract on contact. Rarely, it has caused dermal sensitization. It is apparently poorly absorbed across the skin and the gastrointestinal lining. No cases of systemic poisoning in humans have been reported.

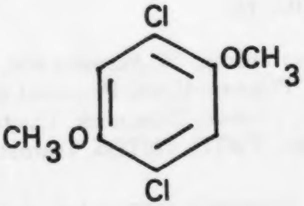
CONFIRMATION OF ABSORPTION OF CHLOROTHALONIL

Chlorothalonil can be measured in blood by gas chromatography, but the analysis is not widely available.

TREATMENT OF CHLOROTHALONIL TOXICOSIS

See **HEXACHLOROBENZENE, TREATMENT OF TOXICOSIS,** Sections 1, 2, and 3 above.

CHLORONEB (Terraneb SP).



Chloroneb is supplied as wettable powder for treatment of soil and seed.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY CHLORONEB

This agent exhibits very low oral toxicity in mammals. It may be moderately irritating to skin and mucous membranes. The metabolite dichloromethoxyphenol is excreted in the urine. No cases of systemic poisoning in humans have been reported.

CONFIRMATION OF ABSORPTION OF CHLORONEB

Chloroneb can be measured in body fluids by chromatography, but the analysis is not widely available.

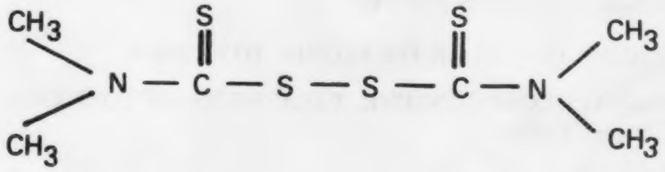
MANAGEMENT OF CHLORONEB EXPOSURE

See **HEXACHLOROBENZENE, TREATMENT OF TOXICOSIS**, Sections 1, 2, and 3 above.

THIOCARBAMATES

Unlike the N-methyl carbamates (Chapter 2), thiocarbamates have very little insecticidal potency. A few exhibit weak anticholinesterase activity, but most have no significant effect on this enzyme. Overall, they are less of a threat to human health than the insecticidal carbamates. Fungicidal thiocarbamates are discussed in this section while those used as herbicides are considered in Chapter 11.

THIRAM



COMMERCIAL PRODUCTS

AAtack, Aules, Chipco Thiram 75, Fermide 850, Fernasan, Hexathir, Mercuram, Nomersam, Polyram-Ultra, Pomarsol forte, Spotrete-F, Spotrete WP 75, Tetrapom, Thimer, Thioknock, Thiotex, Thiramad, Thirasan, Thiuramin, Tirampa, TMTD, TMTDS, Trametan, Tripomol, Tuads, Vancide TM.

Thiocarbamates are commonly formulated as dusts, wettable powders or water suspensions. They are used to protect seeds, seedlings, ornamentals, turf, vegetables, fruit, and apples.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY THIRAM

Thiram dust is moderately irritating to human skin, eyes, and respiratory mucous membranes. Contact dermatitis has occurred in occupationally exposed workers. A few individuals have experienced sensitization to thiram.

Systemic human poisonings by thiram itself have been very few, probably due to limited absorption in most circumstances involving human exposure. Those which have been reported have been similar clinically to toxic reactions to disulfiram (Antabuse), the ethyl analogue of thiram which has been extensively used in alcohol aversion therapy. In laboratory animals, thiram at high dosage has effects similar to those of disulfiram (hyperactivity, ataxia, loss of muscle tone, dyspnea, convulsions), but thiram appears to be about 10 times as toxic as disulfiram.

Clinical doses of disulfiram (0.25–1.00 gm daily) have caused fatigue, headache, dizziness, tremor, restlessness, anorexia, and nausea. Rarely, liver injury, peripheral neuropathy, renal tubular damage, and encephalopathic symptoms have been reported following large and/or protracted dosage. These effects may be due to one or more thiocarbamate biotransformation products (including carbon disulfide) formed in the gut or tissues.

Neither thiram nor disulfiram are cholinesterase inhibitors. Both, however, inhibit the enzyme acetaldehyde dehyrogenase, which is critical to the conversion of acetaldehyde to acetic acid. This is the basis for the "Antabuse" reaction which occurs when ethanol is consumed by a person on regular disulfiram dosage: nausea, vomiting, pounding headache, dizziness, faintness, mental confusion, dyspnea, chest and abdominal pain, profuse sweating, and skin rash. In rare instances, "Antabuse" reactions may have occurred following beverage alcohol ingestion by workers previously exposed to thiram.

CONFIRMATION OF ABSORPTION OF THIRAM

Urinary xanthurenic acid excretion has been used to monitor workers exposed to thiram. The test is not generally available.

TREATMENT OF THIRAM TOXICOSIS

Wash thiram from the skin with soap and water. Flush contamination from the eyes with copious amounts of clean water. If irritation of skin or eyes persists, medical treatment should be obtained.

If a large amount of thiram has been swallowed and effective vomiting has not already occurred, the stomach should be emptied by intubation, aspiration, and lavage, taking all precautions to protect the airway from aspiration of vomitus. Lavage should be followed by instillation of activated charcoal and cathartic (see Chapter 1, TREATMENT, Section 6, page 8). Syrup of Ipecac administration is not advisable because the contained alcohol (2%) may possibly induce an "Antabuse" reaction.

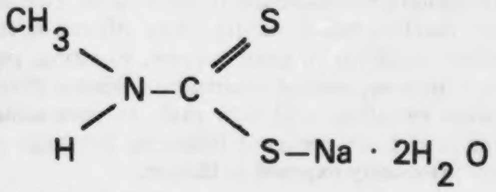
If only a small amount of thiram has been ingested and/or treatment has been delayed, oral administration of activated charcoal and cathartic probably represents optimal management.

In severe poisonings, intravenous infusion of GLUCOSE solution protects the liver and supports mechanisms of detoxication and excretion. If vomiting and diarrhea are severe, fluid balance and serum electrolytes should be monitored, and appropriate electrolyte solutions infused to correct losses.

TREATMENT OF ACETALDEHYDE TOXICOSIS (ANTABUSE REACTION)

OXYGEN inhalation, Trendelenburg positioning, and intravenous fluids are usually effective in relieving manifestations of Antabuse reactions. Persons who have absorbed any significant amount of dithiocarbamate must avoid alcoholic beverages for at least three weeks. Disposition of thiocarbamates is slow and their inhibitory effects on enzymes are slowly reversible.

METAM-SODIUM (METHAM-SODIUM)



COMMERCIAL PRODUCTS

A7 Vapam, Busan 1020, Karbation, Maposol, Metam-Fluid BASF, Nemasol, Solasan 500, Sometam, Trimaton, Vapam, VPM.

Formulated in aqueous solutions for application as a soil biocide to kill fungi, bacteria, weed seeds, nematodes, and insects.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY METAM-SODIUM

Although animal feeding studies do not indicate extraordinary toxicity of metam-sodium by ingestion, its decomposition in water yields methyl isothiocyanate, a gas that is extremely irritating to respiratory mucous membranes, to the eyes, and to the lungs. Inhalation of methyl isothiocyanate may cause pulmonary edema (severe respiratory distress, coughing of bloody, frothy sputum). For this reason, metam-sodium must be used out of doors only, and stringent precautions must be taken to avoid inhalation of evolved gas.

Theoretically, exposure to metam-sodium may predispose the individual to Antabuse reactions if alcohol is ingested after exposure. Such occurrences have not been reported.

CONFIRMATION OF ABSORPTION OF METAM-SODIUM

There are no tests for metam-sodium or its breakdown products in body fluids.

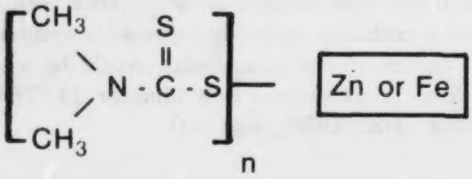
TREATMENT OF METAM-SODIUM TOXICOSIS

Contamination of the skin and eyes should be treated immediately with copious amounts of water to avoid burns and corneal injury. If eye or skin irritation persists, expert medical treatment should be obtained. Poisonings by ingestion of metam-sodium have not been reported. If a large amount has been ingested recently, empty the stomach by gastric intubation, aspiration, and lavage, after taking all precautions to protect the airway (see Chapter 1, TREATMENT, Section 6, page 8). Instill activated charcoal. Also give cathartic unless diarrhea has already commenced.

If pulmonary irritation or edema occur as a result of inhaling methyl isothiocyanate, transport the victim promptly to a medical facility. Treatment for pulmonary edema should proceed as outlined in Chapter 14, FUMIGANTS, page 139.

Metam-sodium is not a cholinesterase inhibitor. Atropine is not antidotal.

ZIRAM AND FERBAM



COMMERCIAL PRODUCTS

Ziram (Carbazinc, Corozate, Cuman, Drupina 90, Fungostop, Hexazir, Mezene, Prodaram, Tricarbamix Z, Triscabol, Zerlate, Vancide MZ 96, Zincmate, Ziram Technical, Ziram F4, Ziram W76, Ziramvis, Zirasan 90, Zirberk, Zirex 90, Ziride, Zitox).

Ferbam (Carbamate, Ferbam, Ferberk, Hexaferb, Knockmate, Trifungol).

These are formulated as flowable and wettable powders, used widely on fruit and nut trees, apples, vegetables, and tobacco.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY ZIRAM AND FERBAM

Dust is irritating to the skin, respiratory tract, and eyes. Prolonged inhalation of ziram is said to have caused neural and visual disturbances, and, in a single case of poisoning, a fatal hemolytic reaction.

If absorbed in sufficient dosage, metallo thiocarbamates may theoretically predispose to an Antabuse reaction following ingestion of alcohol. (See THIRAM.) No occurrences of this have been reported.

CONFIRMATION OF ABSORPTION OF ZIRAM AND FERBAM

No tests for these fungicides or their breakdown products in body fluids are available.

TREATMENT OF ZIRAM AND FERBAM TOXICOSIS

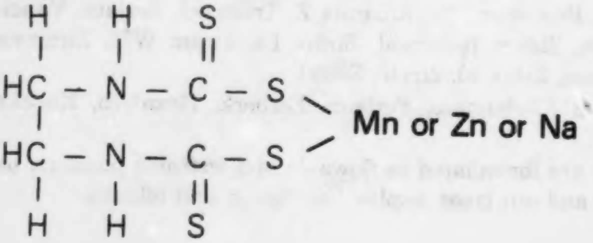
Skin contamination should be washed off with soap and water. Contamination of the eyes should be removed with copious amounts of water. If dermal or eye irritation persists, specialized medical treatment should be obtained.

If substantial amounts of ferbam or ziram have been ingested recently, the stomach should be emptied by gastric intubation, aspiration, and lavage, after all measures have been taken to protect the airway (see Chapter 1, TREATMENT, Section 6, page 8). If dosage was small and/or several hours have elapsed since ingestion, oral administration of charcoal and a cathartic probably represents optimal management.

If hemolysis occurs, intravenous fluids should be administered, and induction of diuresis considered (see Chapter 14, TREATMENT OF NAPHTHALENE TOXICOSIS, page 141).

ETHYLENE BIS DITHIOCARBAMATES (EBDC COMPOUNDS)

MANEB, ZINEB, NABAM, and MANCOZEB



COMMERCIAL PRODUCTS

Maneb (Akzo Chemie Maneb, BASF-Maneb Spritzpulver, Dithane M-22, Kypman 80, Manex 80, Maneba, Manesan, Manex, Manzate, Manzate D, M-Diphar, Polyram M, Remasan Chloroble M, Rhodianebe, Sopranebe, Trimangol, Tubothane, Unicrop Maneb).

Zineb (Aspor, Chem Zineb, Devizeb, Dipher, Dithane Z-78, Hexathane, Kypzin, Lonacol, Parzate, Parzate C, Polyram Z, Tiezene, Tritoftorol, Zebtox, Zineb 75 WP, Zinosan).

Nabam (Chem Bam, DSE, Nabasan, Parzate, Spring Bak).

Maneb and Zineb are formulated as wettable and flowable powders. Nabam is provided as a soluble powder and in water solution.

Mancozeb (manzeb, Dithane M-45, Manzate 200, Akzo Chemie Mancozeb, Mancozin, Manzin, Nemispor, Penncozeb, Policar MZ, Policar S, Vondozeb Plus, Ziman-Dithane). Mancozeb is a coordination product of zinc ion and maneb. It is formulated as a dust and as wettable and liquid flowable powders.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY EBDC COMPOUNDS

These fungicides may cause irritation of the skin, respiratory tract, and eyes. Both maneb and zineb have apparently been responsible for some cases of chronic skin disease in occupationally exposed workers, possibly by sensitization.

Although marked adverse effects may follow injection of EBDC compounds into animals, systemic toxicity by oral and dermal routes is generally low. Nabam exhibits the greatest toxicity, probably due to its greater water solubility and absorbability. Maneb is moderately soluble in water, but mancozeb and zineb are essentially water insoluble. Absorption of the latter fungicides across skin and mucous membranes is probably very limited. Systemic poisonings of humans have been extremely rare. However, zineb apparently precipitated an episode of hemolytic anemia in one worker predisposed by reason of multiple red cell enzyme deficiencies.

The EBDC compounds are not inhibitors of cholinesterase or of acetaldehyde dehydrogenase. They do not induce cholinergic illness or "Antabuse" reactions.

CONFIRMATION OF ABSORPTION OF EBDC COMPOUNDS

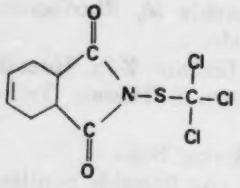
No tests for these fungicides or their breakdown products in body fluids are available.

MANAGEMENT OF EBDC EXPOSURE

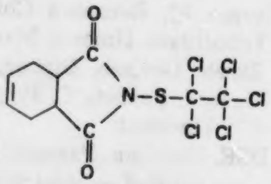
See this chapter, HEXACHLOROBENZENE, TREATMENT OF TOXICOSIS, Sections 1 and 2 above, page 91.

THIOPHTHALIMIDES

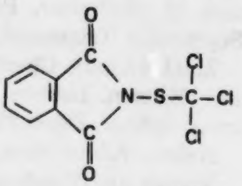
CAPTAN, CAPTAFOL, and FOLPET



CAPTAN



CAPTAFOL



FOLPET

COMMERCIAL PRODUCTS

Captan (Captanex, Captaf, Merpan, Orthocide, Vondcaptan).

Captafol (Crisfolatan, Difolatan, Foltaf, Haipen, Merpafol, Mycodifol, Sanspor).

Folpet (Folpan, Phaltan, Thiophal, Fungitrol II).

These agents are widely used to protect seed, field crops, and stored produce. They are formulated as dusts and wettable powders.

TOXICOLOGY AND ADVERSE EFFECTS OF THIOPHTHALIMIDES

All of these fungicides are moderately irritating to the skin, eyes, and respiratory tract. Dermal sensitization may occur; captafol appears to have been responsible for several episodes of occupational contact dermatitis. No systemic poisonings by thiophthalimides have been reported in man. Laboratory animals given very large doses of captan exhibit hypothermia, irritability, listlessness, anorexia, hyporeflexia, and oliguria, the latter with glycosuria and hematuria.

CONFIRMATION OF ABSORPTION OF THIOPHTHALIMIDES

There are no tests for these fungicides or their breakdown products in body fluids.

MANAGEMENT OF THIOPHTHALIMIDE EXPOSURE

See this chapter, HEXACHLOROBENZENE, TREATMENT OF TOXICOSIS, Sections 1 and 2, above, page 91.

COPPER COMPOUNDS

INORGANIC COPPER COMPOUNDS

Cuprous oxide; cupric oxide; copper hydroxide.

Copper carbonate, basic; copper ammonium carbonate.

Copper acetate; copper sulfate; copper sulfate, tribasic (Bordeaux Mixture); copper oxychloride; copper silicate.

Copper lime dust; copper potassium sulfide.

ORGANIC COPPER COMPOUNDS

Copper linoleate, naphthenate, oleate, phenyl salicylate, quinolinolate, and resinate.

Insoluble compounds are formulated as wettable powders and dusts. Soluble salts are prepared as aqueous solutions. Some organometallic compounds are soluble in mineral oils.

A great many commercial copper-containing fungicides are available. Some are mixtures of copper compounds. Others include lime, other metals, and other fungicides. Compositions of specific products can usually be provided by manufacturers or by poison control centers.

There are several copper-arsenic compounds, such as Paris Green, still used in some agricultures. Toxicity of these is chiefly due to arsenic content (see Chapter 6, ARSENICAL PESTICIDES).

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY COPPER COMPOUNDS

The dust and powder preparations of copper compounds are irritating to the skin, respiratory tract, and particularly to the eyes. The soluble copper salts (such as the sulfate and acetate) are corrosive to mucous membranes and the cornea. Limited solubility and absorption probably account for generally low systemic toxicities of most compounds. The more absorbable organic copper compounds exhibit the greatest systemic toxicity in laboratory animals. While irritant effects from occupational exposures to copper-containing fungicides have been fairly frequent, systemic poisonings of humans have been rare. Most of what is known about mammalian toxicity of copper compounds has come from veterinary toxicology (livestock seem uniquely vulnerable) and rare poisonings in man due to deliberate ingestions of copper sulfate or to consumption of water or food that had been contained in copper vessels. The principal features of poisoning by ingested copper compounds have been 1) gastrointestinal irritation (vomiting and burning pain in the mouth, esophagus and stomach, abdominal pain and diarrhea, sometimes with blood), 2) headache, sweating, weakness, and sometimes shock, 3) liver enlargement and jaundice, 4) hemolysis and methemoglobinemia, and 5) albuminuria, hemoglobinuria, and sometimes acute renal failure.

TREATMENT OF COPPER TOXICOSIS

Contaminating dust and powder should be washed from the skin with soap and water. The eyes should be flushed free of irritating dust, powder, or solution, using clean water or saline. If eye or dermal irritation persists, medical treatment should be obtained. Eye irritation may be severe.

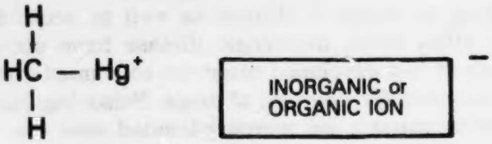
Management of poisonings by ingestion of copper-containing fungicides depends entirely on the chemical nature of the compound: the strongly ionized salts present the greatest hazard; the oxides, hydroxides, oxychloride, and oxysulfate are less likely to cause severe systemic poisoning.

1. Give water or milk as soon as possible to dilute the toxicant and mitigate corrosive action on the mouth, esophagus, and gut.
2. Unless vomiting has been vigorous and effective, empty the stomach by intubation, aspiration, and lavage, taking all precautions to protect the respiratory tract from aspirated stomach contents. (See Chapter 1, TREATMENT, Section 6, page 8). Activated charcoal included in the lavage fluid may be of some value against the organometallic compounds, but is probably less effective against the inorganic copper compounds.

   CAUTION: Gastric intubation may pose a serious risk of esophageal perforation if corrosive action has been severe. In this event, it may be best not to attempt intubation.
3. If indications of systemic illness appear, administer intravenous fluids containing glucose and electrolytes. Monitor fluid balance, and correct blood electrolyte concentrations as needed. If shock develops, give blood transfusions and vasopressor amines, as required.
4. Monitor plasma for evidence of hemolysis (free hemoglobin) and the red cells for methemoglobin. If hemolysis occurs, alkalinize the urine to about pH 7.5 by adding sodium bicarbonate to the intravenous infusion fluid (for dosage, see Chapter 7, TREATMENT, Section 5, page 67). Also, mannitol diuresis may be considered. Unless methemoglobinemia is severe (30–40%), it is probably not advisable to administer methylene blue.
5. Severe pain may require the administration of morphine.
6. The value of chelating agents in copper poisoning has not been established. BAL appears to show some promise in accelerating copper excretion and alleviating illness. If the severity of poisoning appears to warrant its use, a recommended schedule of dosage for initial therapy with BAL and subsequent penicillamine administration is offered in Chapter 6, ARSENICAL PESTICIDES, TREATMENT, Sections 9 and 10, pages 60–61.

ORGANOMERCURY COMPOUNDS

METHYL MERCURY COMPOUNDS

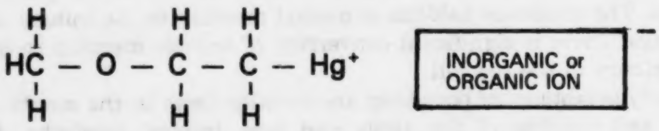


$$\begin{array}{c}\mathrm{H}\\ |\\ \mathrm{HC} - \mathrm{Hg}^{+}\\ |\\ \mathrm{H}\end{array}\quad \boxed{\text{INORGANIC or ORGANIC ION}}^{-}$$

COMMERCIAL PRODUCTS

Methyl mercury hydroxide, nitrile, benzoate, acetate, propionate, pentachlorophenate, quinolinolate.

METHOXYETHYL MERCURY COMPOUNDS

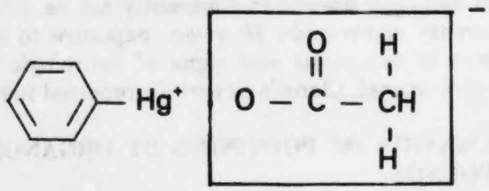


$$\begin{array}{ccccccccc}\mathrm{H} & & & & \mathrm{H} & & \mathrm{H} & & \\ | & & & & | & & | & & \\ \mathrm{HC} & - & \mathrm{O} & - & \mathrm{C} & - & \mathrm{C} & - & \mathrm{Hg}^{+}\\ | & & & & | & & | & & \\ \mathrm{H} & & & & \mathrm{H} & & \mathrm{H} & & \end{array}\quad \boxed{\text{INORGANIC or ORGANIC ION}}^{-}$$

COMMERCIAL PRODUCTS

Methoxyethyl mercury acetate (MEMA, Panogen, Panogen M).
Methoxyethyl mercury chloride (MEMC, Emisan 6, Ceresan).

PHENYL MERCURIC ACETATE



COMMERCIAL PRODUCTS

Agrosan, Cekusil, Celmer, Hong Nien, Liquiphene, Mersolite, Pamisan, Phix, PMAS, Seedtox, Shimmer-ex, Tag HL 331, Unisan.

Setrete (Gallotox, PMAA) is phenyl mercury ammonium acetate. These fungicides have been formulated as aqueous solutions and dusts. They have been used chiefly as seed protectants. Use of alkyl mercury fungicides in the United States has been virtually prohibited for several years. Phenyl mercuric acetate is still used to control diseases of turf, but other applications have been sharply restricted.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY ORGANOMERCURY COMPOUNDS

The mercurial fungicides are among the most toxic pesticides ever developed, in terms of chronic as well as acute hazard. Epidemics of severe, often fatal, neurologic disease have occurred when indigent residents of less developed countries consumed methyl mercury-treated grain intended for planting of crops. Poisoning has also occurred when meat from animals fed mercury-treated seed was eaten. Most of what is known of poisoning by organic mercurial fungicides has come from these occurrences.

Organic mercury compounds are efficiently absorbed across the gut and possibly across the skin. Volatile organic mercury is readily taken up across the pulmonary membrane. Methyl mercury is selectively concentrated in the tissue of the nervous system, and also in the red blood cells. Other alkyl mercury compounds are probably distributed similarly. Excretion occurs almost entirely by way of the bile into the bowel. The residence half-life of methyl mercury in the human is about 70 days. There is significant conversion of organic mercury to inorganic mercury in the red cell.

Early symptoms of poisoning are metallic taste in the mouth, numbness and tingling of the digits and face, tremor, headache, fatigue, emotional lability, and difficulty thinking. Manifestations of more severe poisoning are incoordination, slurred speech, loss of position sense, hearing loss, constriction of visual fields, spasticity or rigidity of muscle movements and deterioration of mental capacity. Many poisonings caused by ingestion of organic mercurials have terminated fatally, and a large percentage of survivors have suffered severe permanent neurologic damage.

Phenyl mercuric acetate is apparently not as extremely toxic as the alkyl mercury compounds. However, exposure to it has preceded the appearance of symptoms and signs of neurologic disease resembling amyotrophic lateral sclerosis in certain reported instances.

CONFIRMATION OF POISONING BY ORGANOMERCURY COMPOUNDS

Mercury content of blood and tissues can be measured by atomic absorption spectrometry. Special procedures are needed for extraction and measurement of organic mercury compounds specifically. These tests are not generally available.

TREATMENT OF ORGANOMERCURY TOXICOSIS

Skin and hair contaminated by mercury-containing dust or solution should be cleansed with soap and water. Eye contamination should be removed by flushing the eye with clean water. If irritation persists, specialized medical care should be obtained.

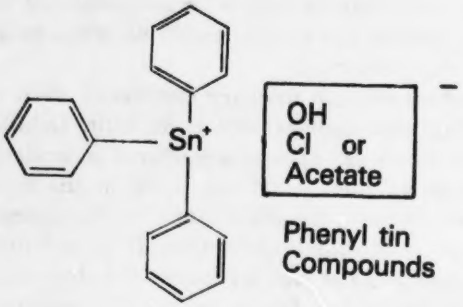
Persons experiencing symptoms (metallic taste in mouth) after inhalation of volatile organic mercury compounds (methyl mercury is the most volatile) should be removed promptly from the contaminated environment, and observed closely for indications of neurologic impairment. Every possible precaution should be taken to avoid exposure to organic mercury compounds.

Ingestion of an organic mercury compound, even at low dosage, is life-threatening, and management is difficult. Detailed discussions of contemporary treatment options are offered in modern clinical toxicology texts. Some of these texts are listed in the introduction to this volume. Following are the basic steps in management of poisoning.

1. Limit gastrointestinal absorption. If a mercurial fungicide has been ingested in the past few hours, the stomach must be evacuated by intubation and lavage, taking all precautions to protect the respiratory tract (see Chapter 1, TREATMENT, Section 6, page 8). Repeated administration of activated charcoal may be beneficial.
2. Administer a **chelating agent**. Dimercaprol (BAL) and EDTA are apparently of little value in poisonings by organic mercury, but other chelators are effective:
   - A. **D-penicillamine**. (This is available in the United States, and has proven effective in reducing the residence half-life of methyl mercury in poisoned humans, see Chapter 6, ARSENICAL PESTICIDES, p. 61, for dosage).
   - B. 2,3-dimercaptopropane-1-sulfonate, and 2,3-dimercaptosuccinic acid. (Although effective, these agents are not currently approved for use in the United States.)
   - C. N-acetyl-D,L-penicillamine. (Effective, but not currently approved for use in the United States.)
3. Extracorporeal hemodialysis and hemoperfusion may be considered, although experience to date has not been encouraging. Although the unmodified organic mercurials are not efficiently dialyzable across most membranes, when used in combination with chelating agents, dialysis may may be of some value in removing organic mercury from the blood (A.H. Al-Abbasi et al. J. Pharmacol. Exptl. Therap. 207:249–254, 1978).

Very little can be done to mitigate neurologic damage caused by organic mercurials.

TRIPHENYL TIN



COMMERCIAL PRODUCTS

Fentin hydroxide (Du-Ter, Duter, Haitin, Phenostat-A H, Suzu-H, TPTH, TPTOH, Triple Tin, Tubotin).

Fentin chloride (Aquatin, Phenostat-C, Tinmate).

Fentin acetate (Batasan, Brestan, Phenostat-A, Phentinoacetate, Suzu, Tinestan, TPTA).

All are formulated as wettable and flowable powders for use mainly as fungicides to control blights on field crops and orchard trees. Fentin chloride is also prepared as an emulsifiable concentrate for use as a molluscicide (Aquatin 20 EC).

Tributyltin salts are used as fungicides and antifouling agents on ships. They are somewhat more toxic by the oral route than triphenyltin, but toxic actions are otherwise probably similar.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY ORGANOTIN COMPOUNDS

These agents are irritating to the eyes, respiratory tract, and skin. They are probably absorbed to a limited extent by the skin and gastrointestinal tract. Manifestations of toxicity are due principally to effects on the brain: headache, nausea, vomiting, dizziness, and sometimes convulsions and loss of consciousness. Photophobia and mental disturbances occur. Epigastric pain is reported, even in poisoning caused by inhalation. Elevation of blood sugar, sufficient to cause glycosuria, has occurred in some cases. The phenyl tin fungicides are apparently less toxic than ethyltin compounds, which have caused cerebral edema, neurologic damage, and death in severely poisoned individuals who were exposed dermally to a medicinal compound of this type. No deaths and very few poisonings have been reported as a result of occupational exposures to phenyltin compounds.

TREATMENT OF ORGANOTIN TOXICOSIS

Skin contamination should be removed by washing with soap and water. Eyes should be flushed free of contaminating material with clean water or saline. If irritation persists, expert medical treatment should be obtained.

If large amounts of phenyltin compound have been ingested in the past few hours, measures should be taken to remove the toxicant from the gastrointestinal tract and to limit absorption (see Chapter 1, TREATMENT, Section 6, p. 8). If oral dosage was small and/or treatment has been delayed, and if the patient is fully alert, oral administration of activated charcoal with a cathartic probably represents optimal management. (See above reference.) Neither BAL, penicillamine, or chelating agents have been effective in lowering tissue stores of organotin compounds in experimental animals.

CADMIUM COMPOUNDS

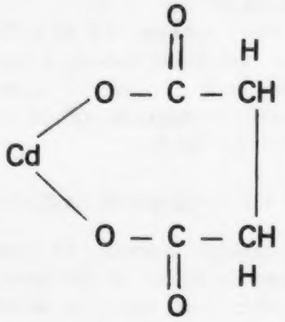
CHEMICAL STRUCTURES

$CdCl_2$

Cadmium Chloride

$CdSO_4$

Cadmium Sulfate



Cadmium succinate

COMMERCIAL PRODUCTS

Cadmium chloride–Caddy, Vi-Cad.
Cadmium sulfate (generic, 14% solution)
Cadmium succinate: Cadminate
Miller 531 and Crag Turf Fungicide 531 are complexes of cadmium, calcium, copper, chromium, and zinc oxides.
Kromad is a mixture of cadmium sebacate, potassium chromate, and thiram.
Cad-Trete is a mixture of cadmium chloride and thiram.

Cadmium salts are used to treat fungal diseases affecting turf and the bark of orchard trees. They are formulated as solutions and emulsions.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY CADMIUM COMPOUNDS

Cadmium salts and oxides are very irritating to the respiratory and gastrointestinal tracts. Inhaled cadmium dust or fume has caused pulmonary edema and pneumonitis, sometimes fatal. Headache, persistent cough, productive of copious frothy and sometimes bloody sputum, is accompanied by labored breathing and chest pain. Fever may follow. Symptoms may persist for weeks. Ingested cadmium causes nausea, vomiting, diarrhea, abdominal pain, and tenesmus. Relatively small inhaled and ingested doses produce serious symptoms. Protracted absorption of cadmium has led to renal damage (proteinuria and azotemia), anemia, liver injury (jaundice), and defective bone structure (pathologic fractures) in chronically exposed persons.

CONFIRMATION OF POISONING BY CADMIUM COMPOUNDS

Cadmium can be measured in body fluids by appropriate extraction, followed by flame absorption spectrometry. The approximate upper limit of blood concentration of cadmium in persons not exceptionally exposed is 10 mcg per liter. Poisoned persons have exhibited blood cadmium concentrations as high as 6,200 mcg per liter and urine cadmium concentrations as high as 2,200 mcg per liter.

It is reported that blood cadmium concentration reflects recent exposure while urine cadmium excretion correlates more closely with body burden. Urinary excretion in excess of 100 mcg per day suggests an unusually high body burden.

TREATMENT OF CADMIUM TOXICOSIS

1. Skin contamination should be removed by washing with soap and water. Contamination of the eyes should be removed by copious flushing with clean water or saline. If irritation persists, medical treatment should be obtained.
2. Respiratory irritation resulting from inhalation of small amounts of cadmium dust may resolve spontaneously, requiring no treatment. More severe reactions, including pulmonary edema and pneumonitis, may require aggressive measures, including positive pressure mechanical pulmonary ventilation, monitoring of blood gases, administration of diuretics, steroid medications, and antibiotics (see Chapter 14, TREATMENT, Sections 2–4, pp. 138–139). Codeine sulfate may be needed to control cough and chest pain.
3. The irritant action of ingested cadmium products on the gastrointestinal tract is so strong that spontaneous vomiting and diarrhea

often eliminate nearly all unabsorbed cadmium from the gut. Give as much milk or egg white orally as the patient will tolerate as soon as possible to neutralize any residual cadmium. Repeat every 4 hours. If retention of some cadmium in the lower GI tract is suspected, administer sorbitol as a cathartic. For dosage, see this chapter, **HEXACHLOROBENZENE, TREATMENT OF TOXICOSIS**, Section 2, page 91.

4. **INTRAVENOUS FLUIDS** may be required to overcome dehydration caused by vomiting and diarrhea. Also, fluids limit cadmium toxicity affecting the kidneys and liver. However, great care must be taken to **MONITOR FLUID BALANCE** and **BLOOD ELECTROLYTE CONCENTRATIONS**, so that failing renal function does not lead to fluid overload.
5. Chelation therapy with calcium disodium EDTA may be considered, depending on measured cadmium in blood and urine, and the status of renal function. Its therapeutic value in cadmium poisoning has not been established, and use of the agent carries the risk that unduly rapid transfer of cadmium to the kidney may precipitate renal failure. Urine protein and blood urea nitrogen and creatinine should be carefully monitored during therapy. A contemporary dosage protocol prescribes 75 mg/kg body weight per day, given in 3-6 divided doses by deep intramuscular injection or slow intravenous infusion for as many as 5 days. Consult a modern clinical toxicology text for details of this therapy.
6. Dimercaprol (BAL) is not recommended for treatment of cadmium poisoning, chiefly because of the risk of renal injury by mobilized cadmium.
7. Monitor urine content of protein and cells regularly and perform liver function tests for indications of injury to these organs.

MISCELLANEOUS ORGANIC FUNGICIDES

Some modern organic fungicides are widely used. Reports of adverse effects on humans are few. Some of the known properties of these agents are listed below.

ANILAZINE (Dyrene, Kemate, Triasyn).

Supplied as wettable and flowable powders. Used on vegetables, cereals, coffee, ornamentals, and turf.

This product has caused skin irritation in exposed workers. Acute oral and dermal toxicities in laboratory animals are low. Human systemic poisonings have not been reported.

BENOMYL (Benlate, Tersan, Benex).

Benomyl is a synthetic organic fungistat having little or no acute toxic effect in mammals. No systemic poisonings have been reported in humans. Although the molecule contains a carbamate grouping, benomyl is not a cholinesterase inhibitor. It is poorly absorbed across skin; that which is absorbed is promptly metabolized and excreted.

Although injuries to exposed individuals have been few, dermal sensitization has occurred in agricultural workers exposed to foliage residues.

CYCLOHEXIMIDE (Acti-dione, Actispray, naramycin).

Cycloheximide is formulated as wettable powders, sometimes combined with other fungicides.

Cycloheximide is a product of fungal culture, effective against fungal diseases of ornamentals and grasses. It is selectively toxic to rats, much less toxic to dogs and monkeys. No human poisonings have been reported. Animals given toxic doses exhibit salivation, bloody diarrhea, tremors, and excitement, leading to coma and death due to cardiovascular collapse. Hydrocortisone increases the rate of survival of deliberately poisoned rats. Atropine, epinephrine, methoxyphenamine, and hexamethonium all relieved the symptoms of poisoning, but did not improve survival.

DODINE (Cyprex, Carpene, Curitan, Melprex, Syllit, Venturol, Vondodine).

Formulated as a wettable powder. Dodine is commonly applied to berries, nuts, peaches, apples, pears, and to trees afflicted with leaf blight.

Dodine is a cationic surfactant with antifungal activity. It is absorbed across the skin. It is irritating to skin, eyes, and gastrointestinal tract. Acute oral and dermal toxicity in laboratory animals is moderate. Poisonings in humans have not been reported. Based on animal studies, ingestion would probably cause nausea, vomiting, and diarrhea.

IPRODIONE (Rovral, Glycophene).

Supplied as wettable powder and other formulations. Used on berries, grapes, fruit, vegetables, grasses, and ornamentals. Also used as seed dressing. Exhibits low acute oral and dermal toxicity in laboratory animals. No human poisonings have been reported.

METALAXYL (Ridomil, Apron 25 WP, Subdue 2E).

Supplied as emulsifiable and flowable concentrates. Used to control soilborne fungal diseases on fruit trees, cotton, hops, soybeans, peanuts, ornamentals, and grasses. Also used as seed dressing. Exhibits low acute oral and dermal toxicity in laboratory animals. No human poisonings have been reported.

TERRAZOLE (Aaterra, Dwell, Ethazol, Koban, Pansoil, Truban).

Supplied as wettable powder and granules for application to soil as a fungicide and nitrification inhibitor. Contact may result in irritation of skin and eyes. Systemic toxicity is low. Human poisonings have not been reported.

THIABENDAZOLE (Apl-Luster, Arbotect, Mertect, TBZ, Tecto, Thibenzole).

Thiabendazole is widely used as an agricultural fungicide, but most experience with its toxicology in humans has come from medicinal use against intestinal parasites. Oral doses administered for this purpose are far greater than those likely absorbed in the course of occupational exposure. Thiabendazole is rapidly metabolized and excreted in the urine, mostly as a conjugated hydroxy-metabolite. Symptoms and signs that sometimes follow ingestion are: dizziness, nausea, vomiting, diarrhea, epigastric distress, lethargy, fever, flushing, chills, rash and local edema, headache, tinnitus, paresthesia, and hypotension. Blood enzyme tests may indicate liver injury. Persons with liver and kidney disease may be unusually vulnerable to toxic effects. Adverse effects from use of thiabendazole as a fungicide have not been reported.

TRIADIMEFON (Bayleton, Amiral).

Supplied as wettable powder, emulsifiable concentrate, suspension concentrate, paste, and dry flowable powder. Used on fruit, cereals, vegetables, coffee, ornamentals, sugarcane, pineapple and turf.

Exhibits moderate acute oral toxicity in laboratory animals, but dermal toxicity is low. Causes irritation if eyes are contaminated. Triadimefon is absorbed across the skin. Overexposures of humans are said to have resulted in hyperactivity followed by sedation.

TRIFORINE (Funginex, Saprol, Denarin, Cela W-524).

Supplied as emulsifiable concentrate and wettable powder. Used on berries, fruit, vegetables, and ornamentals. It is rapidly excreted by mammals, chiefly as a urinary metabolite. It exhibits low acute oral and dermal toxicity in laboratory animals. No human poisonings have been reported.

CONFIRMATION OF ABSORPTION OF ANILAZINE, BENOMYL, CYCLOHEXIMIDE, DODINE, METALAXYL, TERRAZOLE, THIABENDAZOLE, TRIADIMEFON, OR TRIFORINE

There are no generally available laboratory tests for these organic fungicides or their metabolites in body fluids.

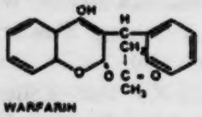
MANAGEMENT OF EXPOSURE TO OR INGESTION OF ANILAZINE, BENOMYL, CYCLOHEXAMIDE, DODINE, METALAXYL, TERRAZOLE, THIABENDAZOLE, TRIADIMEFON, OR TRIFORINE

See treatment protocol in this chapter under HEXACHLOROBENZENE, TREATMENT OF TOXICOSIS, Sections 1 and 2, page 91.

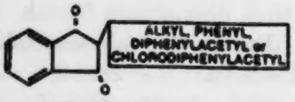
CHAPTER 13

RODENTICIDES

CHEMICAL STRUCTURES

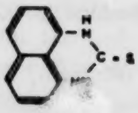


WARFARIN

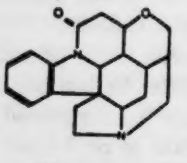


ALKYL, PHENYL, DIPHENYLACETYL or CHLORODIPHENYLACETYL

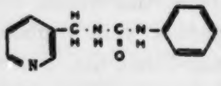
1,3 INDANDIONE



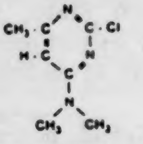
α-NAPHTHYL THIOUREA



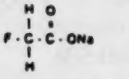
STRYCHNINE



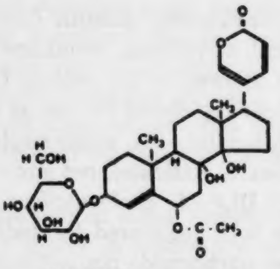
PYRIMINYL



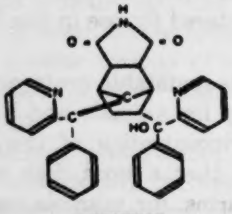
CRIMIDINE



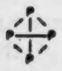
SODIUM FLUOROACETATE



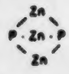
SCILLIROSIDE (Active principle of Red Squill)



NORBORMIDE



YELLOW PHOSPHORUS



ZINC PHOSPHIDE

COMMERCIAL PRODUCTS

Coumarins: warfarin, coumafene, zoocoumarin (Co-Rax, Cov-R-Tox, Kypfarin, Liqua-Tox, RAX, Rodex, Rodex-Blox, Tox-Hid, Warfarin Q), coumafuryl, furmarin, tomarin (Fumarin, Tomarin), coumachlor (Tomorin, Ratilan), bromadiolone (Bromone, Canadien 2000, Contrac, Maki, Ratimus, Tamogam), brodifacoum (Havoc, Klerat, PP581, Ratak Plus, Talon, Volid), difenacoum (Ratak, Neosorexa PP580, WBA 8107), coumatetralyl (Racumin), valone (PMP Tracking Powder), prolin (Eraze, Final, Place-Pax, Warfarin Q Concentrate).

Indandiones: diphacinone, diphacin (Kill-Ko Rat Killer, P.C.Q., Rodent Cake), chlorophacinone (Caid, Drat, Liphadione, LM91, Microzul, Ramucide, Ratomet, Raviac, Rozol, Topitox), pindone, pival, pivaldione (Pivalyn, Pivacin, Tri-ban), radione.

Inorganics: yellow phosphorus, zinc phosphide (Phosvin, Zinc-Tox, ZP, Ridall-Zinc), thallium sulfate. Yellow phosphorus is not sold in the United States. Zinc phosphide is registered, but little used in the United States. Thallium sulfate is no longer registered for pesticidal use.

Convulsants: sodium fluoroacetate (Compound 1080, Fratol, Yasoknock), strychnine, crimidine (Castrix). Only specially trained personnel are allowed to use sodium fluoroacetate or strychnine. Crimidine is no longer registered for use as a pesticide.

Miscellaneous: alpha-naphthyl thiourea (ANTU, Krysid), norbormide (Shoxin, Raticate), red squill (Dethdiet, Rodine), pyriminil (Vacor, RH-787, DLP-87), cholecalciferol (Quintox, Rampage). ANTU and red squill are both registered for rodenticidal use; red squill is little used. Neither norbormide nor pyriminil are now registered for use in the United States.

Rodent poisons are usually added to baits (palatable grain or paste intended to encourage consumption). Safety for animals and humans depends on the toxicity of the agents, concentration of the active ingredient in the bait, and the likelihood that a toxic dose will be consumed by nontarget species. The coumarins, for example, are reasonably effective against pest rodents and they have a good safety record. Rodents are more likely than domestic animals or humans to consume quantities of treated bait that will cause manifest poisoning.

Very small amounts of the extremely toxic rodenticides—sodium fluoroacetate, strychnine, crimidine, yellow phosphorus, zinc phosphide, thallium sulfate—can cause severe and even fatal poisoning. Pyriminil and cholecalciferol are highly toxic agents. The coumarins, indandiones, alpha-naphthyl thiourea, norbormide, and red squill present considerably less hazard to humans and domestic animals.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY COUMARINS AND INDANDIONES

Gastrointestinal absorption of these toxicants is efficient. Warfarin can be absorbed across the skin, but this has occurred only under extraordinary circumstances.

Coumarins and indandiones depress the hepatic vitamin K dependent synthesis of substances essential to blood clotting: prothrombin (factor II) and factors VII, IX and X. The antiprothrombin effect is best known, and is the basis for detection and assessment of clinical poisoning. Concurrently, the agents increase permeability of capillaries throughout the body, predisposing the animal to widespread internal hemorrhage. This generally occurs in the rodent after several days of bait ingestion, although lethal hemorrhage may follow smaller doses of the modern more toxic compounds. Two human fatalities and twelve nonfatal poisonings occurred in Korea in 1953 when a family mistakenly ate warfarin-treated corn meal (0.25 gm %) over several consecutive days. The chief manifestations were nosebleed, bleeding gums, hematuria, melena, and extensive ecchymoses. There is concern that the more toxic modern compounds, such as brodifacoum and difenacoum, may cause serious poisoning of nontarget mammals, including humans, at much lower dosage. In rare instances, anticoagulant rodenticides have apparently caused ecchymoses and skin necrosis for reasons not related to excessive dosage.

Unlike the coumarin compounds, some indandiones cause symptoms and signs of neurologic and cardiopulmonary injury in laboratory rats leading to death before hemorrhage occurs. These actions may account for the greater toxicity of indandiones in rodents. Neither neurologic nor cardiopulmonary manifestations have been reported in human poisonings.

Lengthened prothrombin time from a toxic dose of coumarins or indandiones usually reaches a maximum in 36–72 hours. Lengthened prothrombin time occurs in response to doses much lower than those necessary to cause hemorrhage.

CONFIRMATION OF POISONING BY COUMARINS AND INDANDIONES

Coumarin or indandione poisoning results in an increase in prothrombin time, the result of reduced plasma prothrombin concentration. This is a reliable test for absorption of physiologically significant doses. Detectable reduction in prothrombin occurs within 24–48 hours of ingestion and persists for 1–3 weeks.

TREATMENT OF POISONING BY COUMARINS AND INDANDIONES

1. If amounts of bait ingested were assuredly no more than a few mouthfuls of coumarin- or indandione-treated bait, or a few grains of bait treated with the more toxic brodifacoum or bromadiolone compounds, medical treatment is probably unnecessary.

   A. If there is uncertainty about the amount of bait ingested or the general health of the patient, **PHYTONADIONE** (vitamin K_1) given orally protects against the anticoagulant effect of these rodenticides, with essentially no risk to the patient. Dosage of **PHYTONADIONE:**

      Adults and children over 12 years: 15–25 mg.
      Children under 12 years: 5–10 mg.

      Alternatively, a colloidal preparation of phytonadione, Aquamephyton^R, may be given intramuscularly. For adults and children over 12 years, give 5–10 mg; for children under 12, give 1–5 mg.

   CAUTION: PHYTONADIONE, specifically, is required. Neither vitamin K_3 (menadione, Hykinone^R) nor vitamin K_4 (menadiol) is an antidote for these anticoagulants.

   B. Whatever the dosage, insure that patients (especially children) will be **CAREFULLY OBSERVED** for 4–5 days after ingestion. The indandiones and some of the more recently introduced coumarins may have other toxic effects.

2. If **LARGE AMOUNTS** (1.0–1.5 mg/kg of body weight) of anticoagulant have been ingested within several hours prior to treatment, empty the stomach by giving **SYRUP OF IPECAC**, followed by 1–2 glasses of water. Dosage of **SYRUP OF IPECAC** for adults and children over 12 years: 30 ml; dosage for children under 12 years: 15 ml. Following emesis, give **ACTIVATED CHARCOAL** and **SORBITOL** (see Chapter 1, TREATMENT, Section 6, p. 8 for dosage).

3. If treatment has been delayed several hours following ingestion omit induced emesis, but give activated charcoal and sorbitol orally.

4. If anticoagulant has been ingested any time in the preceding 15 days, determination of the **PROTHROMBIN TIME** provides a basis for judging the severity of poisoning.

   A. If the prothrombin time is significantly lengthened, give Aquamephyton^R, intramuscularly. Dosage for adults and children over 12 years: 5–10 mg; dosage for children under 12 years: 1–5 mg. Decide dose within these ranges according to the degree of prothrombin time lengthening and, in children, the age and weight of the child.

   B. Repeat prothrombin time in 24 hours. If it has not decreased from the original value, repeat Aquamephyton^R dosage.

5. If victim is **BLEEDING** as a result of anticoagulant poisoning, administer Aquamephyton^R intravenously: up to 10 mg in adults and children over 12 years, and up to 5 mg in children under 12 years. Initial dosage should be decided chiefly on the basis of the severity of bleeding. Repeat intravenous Aquamephyton^R in 24 hours if bleeding continues. Inject at rates not exceeding 5% of the total dose per minute. **INTRAVENOUS INFUSION** of the Aquamephyton^R **DILUTED IN SALINE OR GLUCOSE SOLUTION** is recommended. Bleeding is usually controlled in 3-6 hours.

   CAUTION: Adverse reactions, some fatal, have occurred from intravenous phytonadione injections, even when recommended dosage limits and injection rates were observed. For this reason, the **INTRAVENOUS** route should be used **ONLY IN** cases of **SEVERE POISONING.** Flushing, dizziness, hypotension, dyspnea, and cyanosis have characterized adverse reactions.

   A. Antidotal therapy in cases of **SEVERE BLEEDING** should be supplemented with **TRANSFUSIONS** of **FRESH BLOOD** or **FRESH FROZEN PLASMA.** Use of fresh blood or plasma represents the most rapidly effective method of stopping hemorrhage due to these anticoagulants, but the effect may not endure. Therefore, the transfusions should be given along with phytonadione therapy.
   B. Determine **PROTHROMBIN TIMES** and hemoglobin concentrations every 6-12 hours to assess effectiveness of antihemorrhagic measures.
   C. When normal blood coagulation is restored, it may be advisable to drain large hematomata.
   D. Ferrous sulfate therapy may be appropriate in the recuperative period to rebuild lost erythrocyte mass.

INORGANIC RODENTICIDES

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY INORGANIC RODENTICIDES

Yellow phosphorus (also known as white phosphorus) is corrosive to tissues with which it comes in contact, including skin and the gut lining. A few minutes to 24 hours following ingestion, the first symptoms may be burning pain in the throat, chest, and abdomen reflecting severe mucosal injury. Vomiting and diarrhea usually ensue. In some cases, however, lethargy, restlessness, and irritability are the earliest symptoms, followed by symptoms of gastrointestinal injury. Shock often progresses to death in 1-2 days. If the patient survives, a relatively symptom-free period of a few hours or days may occur, followed by indications of severe injury to the liver, myocardium, and brain. These effects may be consequences of phosphine formed in and absorbed from the gut. Nausea and vomiting recur. Hemorrhage at various sites reflects depression of clotting factor synthesis in the damaged liver. Also, thrombocytopenia may contribute. The liver is enlarged and jaundice appears. Shock due to bleeding and toxic myocarditis may be irreversible. Convulsions, delirium, and coma reflect brain injury, to which severe hypoglycemia may contribute. Anuria commonly supervenes due to shock and to the toxic effects of phosphorus products and accumulating bilirubin on renal tubules. Twenty to 50 percent of cases of phosphorus ingestion have terminated fatally.

Zinc phosphide is much less irritating to skin and mucous membranes than yellow phosphorus, but great care must be taken to avoid inhalation of dust, which may induce pulmonary edema. When ingested, the emetic effect of zinc released in the gut may provide a measure of protection. The effects of ingestion are probably the consequences of phosphine and zinc liberated in and absorbed from the gut. Nausea and vomiting, excitement, chills, chest tightness, dyspnea and cough may progress to pulmonary edema. If the patient survives, shock from toxic myocardiopathy, jaundice, and hemorrhage (from liver injury), delirium, convulsions, and coma (from toxic encephalopathy), tetany from hypocalcemia, and anuria from renal tubular damage are all life-threatening manifestations of poisoning.

Thallium sulfate is well absorbed from the gut and across the skin. It exhibits a very large volume of distribution (tissue uptake) and is distributed chiefly to the kidney and liver, both of which participate in thallium excretion. Most blood-borne thallium is in the red cells. Elimination half-life from blood in the adult human is about 1.9 days. A lethal dose for the adult human is probably less than one gram.

The gastrointestinal tract, central nervous system, heart and blood vessels, kidneys, liver, skin, and hair are prominently affected by toxic intakes. One-half to two days following ingestion of a toxic dose, a hemorrhagic gastroenteritis is often manifest as abdominal pain, nausea, vomiting, bloody diarrhea, stomatitis, and salivation. Ileus may appear later on. Headache, lethargy, muscle weakness, paresthesia, tremor, ptosis, ataxia, myoclonic movements, emotional lability, psychosis, convulsions, delirium, and coma reflect toxic encephalopathy, which may be delayed 2–5 days. Fever is a bad prognostic indication of brain damage. Early hypotension is due at least in part to a toxic myocardiopathy; later, hypertension is probably a result of vasoconstriction. The urine may show protein and red cells; high levels of LDH, GOT, ALT, and AST indicate liver injury. Loss of hair (notably, **ALOPECIA**) is a fairly consistent feature of thallium poisoning that is often helpful diagnostically. Death from thallium poisoning may be caused by respiratory paralysis or cardiovascular collapse. Absorption of nonlethal doses of thallium has caused protracted painful neuropathies and paresis, optic nerve atrophy, persistent ataxia and choreiform movements, as well as dementia.

CONFIRMATION OF POISONING BY INORGANIC RODENTICIDES

Phosphorus and phosphides sometimes impart a foul rotten fish odor to vomitus, feces, and sometimes the breath. Luminescence of vomitus or feces is an occasional feature of phosphorus ingestion. Hyperphosphatemia and hypocalcemia occur in some cases, but are not consistent findings.

Thallium can be measured in the serum, urine and hair. Hair analysis is likely to be useful only in establishing protracted prior absorption. Serum concentration does not exceed 30 micrograms per liter in nonexposed persons. Urine concentrations rarely exceed 40 micrograms per liter in the absence of exceptional exposure. Fifty micrograms per kilogram of hair is the approximate upper limit of "normal" in persons not exceptionally exposed. Concentrations roughly 10–100 times these general population levels have been measured in persons clinically poisoned by thallium.

TREATMENT OF POISONING BY YELLOW PHOSPHORUS OR ZINC PHOSPHIDE

1. Brush or scrape nonadherent phosphorus from the skin. **WASH SKIN BURNS** with copious amounts of water. Make sure all particles of phosphorus have been removed. If burned area is infected, cover with an antimicrobial creme.
2. Poisonings by **INGESTED** yellow phosphorus or zinc phosphide are extremely difficult to manage. Treatment is basically supportive and symptomatic.

   CAUTION: Highly toxic phosphine gas may evolve from emesis, lavage fluid, and feces of victims of these poisons. The patient's room should be well ventilated. Persons attending the patient must wear gloves to avoid contact with the phosphorus.

   A. **INTUBATE** and **ASPIRATE** the stomach, after taking all precautions to protect the airway from aspiration of vomitus (Chapter 1, TREATMENT, Section 6, p. 8). **LAVAGE** with several liters of 1:5000 potassium permanganate solution. Catharsis is probably not indicated, but there may be some benefit in administering mineral oil. Dosage is 100 ml for adults and children over 12 years, and 1.5 ml/kg body weight in children under 12 years. Do not give vegetable oils or fats.

   B. Combat shock and acidosis with **TRANSFUSIONS** of whole blood and **INFUSIONS** of glucose and electrolyte solutions. Monitor fluid balance and central venous pressure to avoid fluid overload. Monitor blood electrolytes and pH to guide choice of intravenous solutions. Without administered glucose, hypoglycemia secondary to liver injury may contribute to shock.

C. Administer 100% **OXYGEN** by mask or nasal tube.

D. Combat pulmonary edema with intermittent or continuous **POSITIVE PRESSURE OXYGEN.**

E. **MONITOR URINE** albumin, glucose, and sediment to detect early renal injury. **EXTRACORPOREAL HEMODIALYSIS** will be required if acute renal failure occurs, but it does not enhance excretion of phosphorus. Monitor ECG to detect myocardial impairment. Monitor serum alkaline phosphatase, LDH, ALT, AST, prothrombin time, and bilirubin to evaluate liver damage.

F. Include Aquamephyton^R (vitamin K_1) in intravenous infusions if prothrombin level declines. Dosage of 10–50 mg per day may be required. Administer Aquamephyton^R slowly, intravenously; stop infusion if flushing, cyanosis, paresthesia, hypotension, or dyspnea occurs.

G. **MORPHINE SULFATE,** 8–16 mg subcutaneously every few hours may be necessary to control pain. Child's dose: 0.1–0.2 mg/kg body weight.

H. **CONTROL CONVULSIONS.** See Chapter 3, TREATMENT, Section 4, p. 21.

TREATMENT OF POISONING BY THALLIUM SULFATE

1. If thallium sulfate was swallowed less than a few hours prior to treatment, and if the patient is fully alert, empty the stomach by administering **SYRUP OF IPECAC,** followed by 1-2 glasses of water. Dosage for adults and children over 12 years: 30 ml; dosage for children under 12 years: 15 ml. Put in place a cuffed endotracheal tube to protect the airway, then intubate the stomach and lavage with 1% sodium or potassium iodide, to form insoluble thallium iodide. Instill a slurry of **ACTIVATED CHARCOAL** (for dosage, see Chapter 1, TREATMENT, Section 6, p. 8). Include sorbitol with the charcoal unless diarrhea is already in progress.
2. If treatment is long delayed, administer the activated charcoal orally. Include sorbitol unless diarrhea has already commenced. Repeated administration of charcoal may be of benefit in hastening elimination of thallium. Give half or more of the original dosage every 2–4 hours.
3. Give **ELECTROLYTE** and **GLUCOSE** solutions by intravenous infusion to support urinary excretion of thallium by diuresis. Monitor fluid balance carefully to insure that fluid overload does not occur. If shock develops, give whole blood, plasma, or plasma expanders. Pressor amines must be used very carefully in light of myocardial injury. Monitor ECG for arrhythmias.
4. Inclusion of **POTASSIUM CHLORIDE** in the infusion fluid displaces thallium from cells into the extracellular compartment and thereby accelerates excretion. Care must be taken, however, that

excessive redistribution of thallium to the brain does not occur. Concentration of potassium in the infusion fluid should probably not exceed 10 milliequivalents per liter. Monitor clinical status carefully, and stop KCl administration if encephalopathy worsens.

5. **CONTROL CONVULSIONS** and myoclonic jerking. For dosages of anticonvulsants, see Chapter 3, TREATMENT, Section 4, p. 21. Benzodiazepines (diazepam or lorazepam) are the preferred agents in thallium poisoning. In at least one case, neurologic status deteriorated when barbiturates were administered.
6. **COMBINED HEMODIALYSIS AND HEMOPERFUSION** has proven moderately effective in reducing the body burden of thallium in victims of severe poisoning. In one case, peritoneal dialysis was not effective.
7. Several methods for chelating and/or accelerating disposition of thallium have been tested and found either relatively ineffective or hazardous. Chelating agents are not recommended in thallium poisoning.
8. Potassium ferric ferrocyanide (Prussian Blue) orally enhances fecal excretion of thallium by exchange of potassium for thallium in the gut. However, it is not approved for human use, and suitably pure material is not generally available for medicinal purposes.

CONVULSANTS

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY CONVULSANT RODENTICIDES

Sodium fluoroacetate is readily absorbed by the gut, but only to a limited extent across skin. The toxic mechanism is distinct from that of fluoride salts. Three molecules of fluoroacetate are combined in the liver to form a molecule of fluorocitrate, which poisons critical enzymes of the tricarboxylic acid cycle, thus impairing cellular respiration. The heart and the brain are the organs most prominently affected. The effect on the heart is to cause arrhythmias, progressing to ventricular fibrillation, which is the usual cause of death. Neurotoxicity is expressed as violent tonic-clonic convulsions, spasms and rigor, sometimes not occurring for hours after ingestion.

Strychnine is a natural toxin (nux vomica) which causes violent epileptiform convulsions by direct excitatory action on the cells of the central nervous system, chiefly the spinal cord. Death is caused by convulsive interference with pulmonary function, by depression of respiratory center activity, or both. Strychnine is detoxified in the liver. Residence half-life is about 10 hours in humans. Onset of symptoms is usually within 15–20 minutes of ingestion. Lethal dose in humans is 5–8 mg/kg body weight.

Crimidine is a synthetic chlorinated pyrimidine compound which, in adequate dosage, causes violent convulsions similar to those produced by strychnine.

CONFIRMATION OF POISONING BY CONVULSANT RODENTICIDES

There are no generally available tests to confirm poisoning by the convulsant rodenticides.

TREATMENT OF POISONING BY SODIUM FLUOROACETATE

Sodium fluoroacetate poisonings have occurred almost entirely as a result of accidental and suicidal ingestions. If the poison was ingested shortly before treatment and convulsions have not yet occurred, the first step in treatment is to remove the toxicant from the gut. If the victim is already convulsing, however, it is necessary first to control the seizures before gastric lavage and catharsis are undertaken.

1. **CONTROL CONVULSIONS** by giving **OXYGEN**, and administering **ANTICONVULSANT** medications (see Chapter 3, TREATMENT, Section 4, page 21). Seizure activity from fluoroacetate may be so severe that doses necessary for seizure control may paralyze respiration. For this reason, it is best to **INTUBATE THE TRACHEA** as early as possible in the course of seizure control, and support pulmonary ventilation mechanically. This has the added advantage of protecting the airway from aspiration of regurgitated gastric contents.
2. Empty the stomach by **INTUBATION, ASPIRATION,** and **LAVAGE** with isotonic saline or tap water (Chapter 1, TREATMENT, Section 6, page 8). There is probably very little adsorption of sodium fluoroacetate on activated charcoal. Instill **SORBITOL** as a cathartic before withdrawing the stomach tube (see reference above for dosage).
3. Administer **INTRAVENOUS FLUIDS** cautiously to support excretion of absorbed fluoroacetate. It is especially important to avoid fluid overload in the presence of a weak and irritable myocardium.
4. Monitor **ELECTROCARDIOGRAM** for arrhythmias and, if detected, treat with an appropriate antiarrhythmic drug. Consult package inserts for dosages and recommended methods for administration. Facilities for electroshock **CARDIOVERSION** should be at hand. Some victims of fluoroacetate poisoning have been rescued after repeated cardioversions.
5. **CALCIUM GLUCONATE** (10% solution) given slowly intravenously should be given to relieve carpopedal spasm. Care must be taken to avoid extravasation.

Dosage of CALCIUM GLUCONATE:

Adults and children over 12 years: 10 ml of 10% solution, given slowly, intravenously. Repeat if necessary.

Children under 12 years: 0.05 gm (one-half ml of 10% solution) per kg body weight, preferably included in intravenous infusion fluid. Repeat dosage as needed.

TREATMENT OF POISONING BY STRYCHNINE OR CRIMIDINE

Strychnine and crimidine cause violent convulsions shortly following ingestion of toxic doses. Both poisons are probably well adsorbed on charcoal. If the patient is seen fully conscious and not convulsing a few moments after the ingestion, great benefit may derive from the immediate ingestion of **ACTIVATED CHARCOAL** (see Chapter 1, TREATMENT, Section 6, page 8 for dosage). If the patient is already obtunded or convulsing, the involuntary motor activity must be controlled before steps are taken to empty the gut and limit toxicant absorption.

1. **CONTROL CONVULSIONS.** See Chapter 3, TREATMENT, Section 4, page 21.
2. **LIMIT TOXICANT ABSORPTION** from the gut. Induced emesis is hazardous because of the risk of aspiration of vomitus when seizures begin. As soon as possible, protect the airway, preferably with a cuffed **ENDOTRACHEAL TUBE,** then remove stomach contents by **ASPIRATION** and **LAVAGE** with a slurry of activated charcoal (see Chapter 1, TREATMENT, Section 6, page 8). Repeated doses of activated charcoal may be beneficial, giving half or more the initial dose every 2–4 hours.
3. Administer intravenous fluids to support excretion of absorbed toxicants. Mannitol diuresis may be considered, and inclusion of sodium bicarbonate in the infusion fluid counteracts metabolic acidosis generated by convulsions. Effectiveness of hemodialysis and hemoperfusion has not been tested.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY: ANTU, NORBORMIDE, RED SQUILL, PYRIMINYL, AND CHOLECALCIFEROL

Alpha-naphthyl thiourea (ANTU) appears to have unique toxic effects on Norway rats. Although dogs are somewhat susceptible, other species, including man, are resistant to the toxicity of ANTU. Poisoned Norway rats die of pulmonary edema and pleural effusion. Several humans poisoned by deliberate ingestion of ANTU (and chloralose) developed severe short-lived tracheobronchial hypersecretion, but apparently not pulmonary edema. Although some persons required mechanically assisted pulmonary ventilation, the reaction, in most cases, resolved in a few hours.

Norbormide is a single-dose synthetic organic compound uniquely toxic to Norway and roof rats, in which it causes an intense generalized vasoconstriction, leading to death from tissue anoxia. The most severe effects observed in human volunteers ingesting 20-300 mg orally were a brief and moderate lowering of body temperature and a mild lowering of systolic blood pressure. These effects, which were observed in the absence of symptoms, were maximal at one hour and were not apparent two hours after ingestion.

Red squill is an ancient rodenticide, consisting of the inner portions of a small cabbage plant grown in eastern Mediterranean countries. The toxic properties are probably due to cardiac glycosides. For several reasons, mammals other than rodents are unlikely to be poisoned: 1) red squill is intensely nauseant, so that animals which vomit (rodents do not) are unlikely to retain the poison; 2) the glycoside is not efficiently absorbed from the gut; 3) absorbed glycoside is rapidly excreted. Injection of the glycosides leads to effects typical of digitalis: alterations in cardiac impulse conduction and arrhythmias.

Pyriminil (Vacor) is a substituted urea compound that is toxic to mammals, including humans, by effects on multiple organs and tissues. It causes severe damage to central and peripheral nervous systems, including both somatic and autonomic components of the latter. It destroys beta cells of the pancreas, leading to insulin-deficient diabetes mellitus. Cardiac arrhythmias probably reflect injury to the impulse conduction system. Nicotinamide antagonism is a likely biochemical basis for many of the toxic effects.

Most severe poisonings have resulted from suicidal ingestions. Early manifestations of poisoning are abdominal pain, nausea, vomiting, lethargy, confusion, visual disturbances, painful paresthesia, urinary retention (or frequency), and orthostatic hypotension (fainting when sitting up or standing from the reclining position). Later effects are paresis of the limbs, areflexia, ataxia, persistent anorexia, and bowel dystonias. Early hypoglycemia progresses to hyperglycemia, often accompanied by ketoacidosis. Severe and prolonged orthostatic hypotension is characteristic. Death may result from cardiac arrhythmias, diabetic ketoacidosis, inanition, or aspiration pneumonia.

Cholecalciferol is the activated form of vitamin D (vitamin D_3). Its toxic effect is probably a combination of actions on liver, kidney, and possibly the myocardium, the last two toxicities being the result of hypercalcemia. Early symptoms and signs of vitamin D-induced hypercalcemia in humans are fatigue, weakness, headache, and nausea. Polyuria, polydipsia, proteinuria, and azotemia result from acute renal tubular injury by hypercalcemia. This is commonly the cause of death. Prolonged hypercalcemia results ultimately in nephrolithiasis and nephrocalcinosis. Azotemia occurs as renal tubular damage progresses.

CONFIRMATION OF POISONING BY MISCELLANEOUS RODENTICIDES

Cholecalciferol intoxication is indicated by an elevated concentration of calcium (chiefly the unbound fraction) in the serum.

There are no generally available tests for the other rodenticides or their biotransformation products.

TREATMENT OF POISONING BY ALPHA NAPHTHYL THIOUREA (ANTU)

Alpha naphthyl thiourea is unlikely to cause severe poisoning unless large amounts have been ingested. If a small amount has been ingested, or if treatment has been delayed, administer **ACTIVATED CHARCOAL** and **SORBITOL** orally (see Chapter 1, TREATMENT, Section 6, p. 8 for dosage).

If a large quantity was ingested, take steps to protect the airway, then empty the stomach by **INTUBATION, ASPIRATION,** and **LAVAGE.** Instill **ACTIVATED CHARCOAL** and **SORBITOL** before withdrawing the tube (see Chapter 1, TREATMENT, Section 6, p. 8).

If dyspnea develops, support pulmonary ventilation mechanically using oxygen. Although not tested for efficacy or safety, careful intravenous injection of aminophylline might be used to relieve bronchospasm and bronchorrhea. See package insert for dosage.

TREATMENT OF POISONING BY NORBORMIDE

Norbormide is unlikely to cause human poisoning unless extraordinary amounts have been ingested. In this event, give activated charcoal and sorbitol orally (for dosage, see Chapter 1, TREATMENT, Section 6, p. 8). Monitor body temperature and blood pressure. Use warm blankets to correct hypothermia. A recumbent position and cautious doses of a pressor drug may be used to correct hypotension, if this develops. To date, no human poisonings by norbormide have occurred, and therefore, therapeutic procedures have not been tested.

TREATMENT OF POISONING BY RED SQUILL

Red squill is unlikely to cause poisoning unless ingested at substantial dosage. The problem is usually self-correcting due to its intense emetic effect. If, for some reason, the squill is retained, Syrup of Ipecac, followed by 1-2 glasses of water, should be administered to initiate vomiting. Dosage for adults and children over 12 years: 30 ml; dosage for children under 12 years: 15 ml. When vomiting stops, administer activated charcoal and sorbitol (see Chapter 1, TREATMENT, Section 6, p. 8 for dosages). Monitor cardiac status electrocardiographically.

TREATMENT OF POISONING BY PYRIMINYL

Pyriminyl poisonings have resulted from accidental and suicidal ingestions. Severe effects have sometimes been caused by very small doses. Immediate measures to limit absorption are essential.

1. If pyriminyl was ingested, and if the patient is fully conscious, administer **SYRUP OF IPECAC** followed by several glasses of water to induce emesis. Dosage for adults and children over 12 years: 30 ml; dosage for children under 12 years: 15 ml.
   If there is reason to believe some pyriminyl remains in the stomach, protect the airway with a cuffed endotracheal tube, then **INTUBATE, ASPIRATE,** and **LAVAGE** the stomach with a slurry of **ACTIVATED CHARCOAL** (see Chapter 1, TREATMENT, Section 6, p. 8 for dosage). Leave activated charcoal and sorbitol in the stomach before withdrawing the lavage tube. Repeated doses of charcoal may well be beneficial, giving half or more of the initial dose every 2-4 hours.
2. Monitor blood and urine glucose concentrations, serum alkaline phosphatase, amylase, LDH, AST, and ALT activities, urine ketone concentrations, blood electrolytes, and BUN. Examine the electrocardiogram for arrhythmias.
3. Infuse **ELECTROLYTE SOLUTIONS** intravenously to accelerate toxicant excretion and correct errors in specific electrolyte concentrations. If ketoacidosis appears, include sodium bicarbonate or Ringer's-lactate to control acidosis.
4. If **DIABETIC KETOACIDOSIS** appears (ketonuria, metabolic acidosis, hyperglycemia), administer enough regular insulin to control the acidosis and hyperglycemia, as in naturally occurring diabetic ketosis. The diabetes resulting from pyriminyl tends to be brittle and correspondingly difficult to control.
5. The sequelae of pyriminyl poisoning are essentially irreversible. The diabetes may be controlled with insulin, or, in mild cases,

sulfonylurea drugs. Orthostatic hypotension may be alleviated by support stockings, sympathomimetic drugs, or dihydroergotamine.

TREATMENT OF POISONING BY CHOLECALCIFEROL

Cholecalciferol at high dosage may cause severe poisoning and death. Human poisonings from its use as a rodenticide have not been reported, but vitamin D overdosage has occurred under clinical circumstances. Treatment is directed at limiting gastrointestinal absorption, accelerating excretion, and counteracting the hypercalcemic effect.

1. If cholecalciferol has been ingested within a few hours prior to treatment, and if the patient is fully alert, induce emesis by **SYRUP OF IPECAC**, followed by 1-2 glasses of water. Dosage for adults and children over 12 years: 30 ml; dosage for children under 12 years: 15 ml. When vomiting stops, give **ACTIVATED CHARCOAL** and **SORBITOL** (for dosage, see Chapter 1, TREATMENT, Section 6, p. 8). Repeated administration of charcoal at half or more the initial dosage every 2-4 hours may be beneficial.
2. Administer intravenous fluids (normal saline or 5% glucose) at moderate rates to support excretory mechanisms and excretion. **MONITOR FLUID BALANCE** to avoid overload, and measure serum electrolytes periodically. Measure total and ionized calcium levels in the blood 24 hours after cholecalciferol ingestion to determine severity of toxic effect. Monitor urine for protein, red and white cells to assess renal injury.
3. **FUROSEMIDE** (Lasix), 20-40 mg intravenously, or 40-120 mg daily by mouth may be given to promote diuresis. Dosage for children under 12 is approximately 0.5-1.0 mg/kg body weight intravenously, 1.0-2.0 mg/kg body weight orally. Monitor serum potassium after dosage; give potassium chloride if hypokalemia occurs. Consult package insert for additional directions and warnings.
4. **PREDNISONE** and similar glucocorticoids reduce elevated blood calcium levels in certain diseases. Although they have not been tested in cholecalciferol overdosage, it is possible that they would be beneficial. Dosage is approximately 1 mg per kilogram per day, to a maximum of 20 mg per day.
5. **CALCITONIN** (salmon calcitonin, Calcimar^{R}) is a logical antidote for cholecalciferol actions, but has not been tested in human poisoning. In other conditions, the usual dosage is 4 International Units per kg body weight every 12 hours, by intramuscular or subcutaneous injection, continued for 2-5 days. The dose may be doubled if calcium lowering effect is not sufficient. Calcium gluconate (10%) for intravenous injection should be immediately available if indications of hypocalcemia (carpopedal spasm, cardiac arrhythmias) appear. Consult package insert for additional directions and warnings.

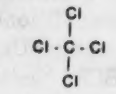
6. **If total serum calcium is markedly elevated (more than about 8 milliequivalents per liter) the intravenous infusion of disodium edetate (EDTA) may be considered. Although this agent is very effective in reducing the level of physiologically active serum calcium by chelation, only moderate overdosage may lead to hypocalcemia, tetany, ventricular arrhythmias, respiratory arrest, and death. A daily dose of 50 mg/kg body weight, to a maximum of 3 gm, may be infused in 500 ml of 5% glucose or 0.9% saline over at least 4–6 hours, while the ECG and serum calcium are being monitored. Calcium gluconate (10%) should be immediately at hand to reverse hypocalcemia if arrhythmias or carpopedal spasm appear. Disodium edetate is CONTRAINDICATED if there are any signs of renal insufficiency, congestive heart failure, or hypokalemia (less than 3.5 milliequivalents per liter). Consult package insert for additional directions and warnings.**

CHAPTER 14

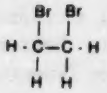
FUMIGANTS

CHEMICAL STRUCTURES

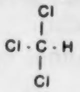
HALOCARBONS



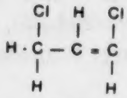
Carbon Tetrachloride



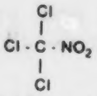
Ethylene Dibromide



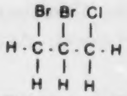
Chloroform



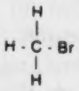
1,3-Dichloro-propane



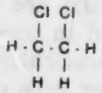
Chloropicrin



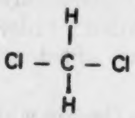
Dibromo-chloropropane



Methyl Bromide

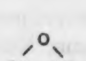


Ethylene Dichloride

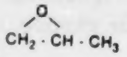


Methylene Chloride

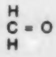
OXIDES AND ALDEHYDES



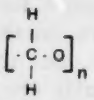
Ethylene Oxide



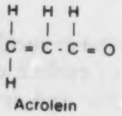
Propylene Oxide



Formaldehyde



Paraformaldehyde



Acrolein

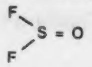
SULFUR AND PHOSPHORUS COMPOUNDS

$O = S = O$

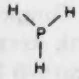
Sulfur Dioxide

$S = C = S$

Carbon Disulfide



Sulfuryl Fluoride

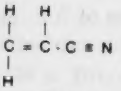


Phosphine (from $Al \equiv P + H_2O$)

CYANIDES

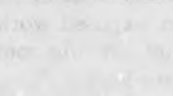
$H \cdot C \equiv N$

Hydrogen Cyanide

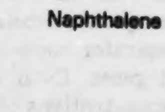


Acrylonitrile

Hydrocarbon-



Paradichlorobenzene



Naphthalene

COMMERCIAL PRODUCTS

Hydrocarbon: naphthalene (naphthene).

Halocarbons: methylene chloride, methyl bromide (bromomethane, Brom-O-Gas, Brom-O-Sol, Meth-O-Gas, Terr-O-Gas, Brom-O-Gaz, Celfume, Kayafume, MeBr), chloroform (trichloromethane), carbon tetrachloride, chloropicrin (nitrochloroform, Chlor-O-Pic, Aquinite, Dojyopicrin, Dolochlor, Larvacide, Pic-Clor, Tri-Clor), ethylene dichloride (dichloroethane, EDC), ethylene dibromide (dibromoethane, Bromofume, Celmide, E-D-Bee, EDB, Kopfume, Nephis), dichloropropene (Telone II Soil Fumigant, D-D92), dichloropropene plus dichloropropane (D-D), dibromochloropropane (Nemafume, Nemanax, Nemaset, DBCP, Nematocide), paradichlorobenzene (PDB, Paracide).

Oxides and Aldehydes: ethylene oxide (epoxyethane, ETO, oxirane), propylene oxide, formaldehyde (formalin is a 40% aqueous solution), paraformaldehyde, acrolein (propenal, acrylaldehyde, Aqualin).

Sulfur Compounds: sulfur dioxide, sulfuryl fluoride (Vikane), carbon disulfide.

Phosphorus Compounds: phosphine (liberated from aluminum phosphide: phostoxin, AlP, Fumitoxin).

Nitrogen Compounds: hydrogen cyanide (hydrocyanic acid, prussic acid, Cyclon), acrylonitrile (Acritet, Carbacryl, Acrylofume—all mixtures with carbon tetrachloride).

Packaging and formulation of fumigants is complex. Those which are gases at room temperature (methyl bromide, ethylene oxide, sulfur dioxide, hydrogen cyanide, sulfuryl fluoride) are provided in compressed gas cylinders. Liquids are marketed in cans or drums. Solids which sublime, such as naphthalene and paradichlorobenzene, must be packaged so as to prevent significant contact with air before they are used.

Mixtures of fumigants have several advantages. Carbon tetrachloride reduces the explosiveness of carbon disulfide and acrylonitrile. Chloropicrin, having a strong odor and irritant effect, is often added as a "warning agent" to other liquid fumigants.

Liquid halocarbons and carbon disulfide evaporate into the air while naphthalene and paradichlorobenzene sublime. Paraformaldehyde slowly depolymerizes to formaldehyde. Aluminum phosphide slowly reacts with water vapor in the air to liberate phosphine, an extremely toxic gas.

Fumigants have remarkable capacities for diffusion (a property essential to their function). Some readily penetrate rubber and neoprene personal protective gear, as well as human skin. They are rapidly absorbed across the pulmonary membrane, gut, and skin. Special adsorbents are required in respirator canisters to protect exposed workers from airborne fumigant gases. Even these may not provide complete protection when air concentrations of fumigants are high.

TOXICOLOGY AND MANIFESTATIONS OF POISONING

Naphthalene is a solid white hydrocarbon long used in ball, flake, or cake form as a moth repellant. It sublimes slowly. The vapor has a sharp, pungent odor that is irritating to the eyes and upper respiratory tract. Inhalation of high concentrations causes headache, dizziness, nausea, and vomiting. Intensive prolonged inhalation exposure, or ingestion or dermal exposure (from contact with heavily treated fabric) may cause hemolysis, particularly in persons afflicted with glucose-6-phosphate dehydrogenase deficiency. It is actually the alpha-naphthol metabolite that causes the hemolysis. Secondary renal tubular damage may ensue from the naphthol and from the products of hemolysis. Convulsions and coma may occur, particularly in children. In infants, high levels of hemoglobin, methemoglobin, and bilirubin in the plasma may lead to encephalopathy (kernicterus). Some individuals exhibit dermal sensitivity to naphthalene.

Methylene chloride is one of the less toxic halocarbons. It is absorbed by inhalation and to a limited extent across the skin. Exposure to high concentrations may cause central nervous system depression, manifest as fatigue, weakness, and drowsiness. Some absorbed methylene chloride is degraded to carbon monoxide in humans, yielding increased blood concentrations of carboxyhemoglobin. However, concentrations are rarely high enough to cause symptoms of carbon monoxide poisoning. Ingestion has caused death from gastrointestinal hemorrhage, severe liver damage, coma, shock, metabolic acidosis, and renal injury. In laboratory animals, extraordinary dosage has caused irritability, tremor, and narcosis, leading to death.

Methyl bromide is colorless and nearly odorless, but is severely irritating to the lower respiratory tract, sometimes inducing pulmonary edema, hemorrhage, or a confluent pneumonia. The onset of respiratory distress may be delayed 4-12 hours after exposure. It is a central nervous system depressant, but may also cause convulsions. Early symptoms of acute poisoning include headache, dizziness, nausea, vomiting, tremor, and ataxia. Repeated prolonged exposures in some cases have led to a long-lasting syndrome of ataxia, incoordination, muscle weakness and areflexia. One case of recurrent myoclonic seizures has been reported which required treatment for five years following methyl bromide exposure. If liquid methyl bromide contacts the skin, severe burning, itching, and blister formation occurs. Skin necrosis may be deep and extensive.

Chloroform has an agreeable sweet odor and is only slightly irritating to the respiratory tract. It is a powerful central nervous system depressant (in fact, an anesthetic). Inhalation of toxic concentrations in air leads to dizziness, loss of sensation and motor power, and then unconsciousness. Inhalation of large amounts causes cardiac arrhythmias, sometimes progressing to ventricular fibrillation. Large absorbed doses damage the functional cells of the liver and kidney. Ingestion is more likely to cause serious liver and kidney injury than is inhalation of the vapor.

Carbon tetrachloride is less toxic than chloroform as a central nervous system depressant, but is much more severely hepatotoxic, particularly following ingestion. Liver cell damage is apparently due to a free radical generated in the process of initial dechlorination. Kidney injury also occurs; sometimes this is exaggerated by jaundice. Cardiac arrhythmias, progressing to fibrillation, may follow inhalation of high concentrations of carbon tetrachloride or ingestion of the liquid.

Chloropicrin is severely irritating to the upper respiratory tract, eyes, and skin. Inhalation of an irritant concentration sometimes leads to vomiting. Ingestion could be expected to cause a corrosive gastroenteritis.

Ethylene dichloride (correctly, dichloroethane) is moderately irritating to the eyes and respiratory tract. It depresses the central nervous system, induces cardiac arrhythmias, and damages the liver and kidney, in much the same way as carbon tetrachloride. Symptoms and signs of poisoning include headache, nausea, vomiting, dizziness, diarrhea, hypotension, cyanosis, and unconsciousness. In addition to necrosis of liver and kidney cells, the adrenal cortex may be destroyed, especially after poisoning by ingestion.

Ethylene dibromide (correctly, dibromoethane) is a severe irritant to skin, eyes, and respiratory tract. The liquid causes blistering and erosion of skin, and is corrosive to the eyes. Once absorbed, it may cause pulmonary edema and central nervous system depression. Long-term exposure may have some damaging effect on testicular tissue. Persons poisoned by ingestion have suffered chemical gastroenteritis, liver necrosis, and renal tubular damage. Death is usually due to respiratory or circulatory failure. A powerful disagreeable odor is advantageous in warning occupationally exposed workers of the presence of this gas.

Dibromochloropropane is irritating to skin, eyes, and the respiratory tract. Eye damage has resulted from repeated exposure to the vapors. When absorbed, it causes headache, nausea, vomiting, ataxia, and slurred speech. Liver and kidney damage are prominent features of acute poisoning. Chronic exposure to relatively low concentrations has led to permanent sterility of workers in a manufacturing plant, by causing diffuse necrosis of seminiferous tubule cells. Because it is much less odiferous than ethylene dibromide, exposure of workers to toxic concentrations of DBCP is more likely.

Dichloropropene and **dichloropropane** are strongly irritating to the skin, eyes, and respiratory tract. Bronchospasm may result from inhalation of high concentrations. Liver, kidney, and cardiac toxicity is probably similar to that produced by carbon tetrachloride.

Paradichlorobenzene is solid at room temperature, and is now widely used as a moth repellant, air freshener, and deodorizer in homes and in public facilities. The vapor is only mildly irritating to the nose and eyes. Liver injury and tremor may occur following ingestion of large amounts. Although accidental ingestions, especially by children, have been fairly common, symptomatic human poisonings have been rare. Other stereoisomers of dichlorobenzene are more toxic than the para-isomer.

Ethylene oxide and **propylene oxide** are irritants to all tissues they contact. Aqueous solutions of ethylene oxide cause blistering and erosion of the affected skin. The area of skin may thereafter be sensitized to the fumigant. Inhalation of high concentrations is likely to cause pulmonary edema and cardiac arrhythmias. Headache, nausea, vomiting, weakness, and a persistent cough are common early manifestations of acute poisoning. Coughing of bloody, frothy sputum is characteristic of pulmonary edema.

Airborne **formaldehyde** is irritating to the eyes and to membranes of the upper respiratory tract. In some individuals, it is a potent sensitizer, causing asthma and dermatitis. High air concentrations may cause laryngeal edema, asthma, or tracheobronchitis, but apparently not pulmonary edema. Aqueous solutions in contact with the skin cause hardening and roughness, due to superficial coagulation of the keratin layer. Ingested formaldehyde attacks the lining membrane of the stomach and intestine, causing necrosis and ulceration. Absorbed formaldehyde is rapidly converted to formic acid. The latter is partly responsible for the metabolic acidosis that is characteristic of formaldehyde poisoning. Circulatory collapse and renal failure may follow the devastating effects of ingested formaldehyde on the gut, leading to death. Paraformaldehyde is a polymer which slowly releases formaldehyde into the air. Toxicity is somewhat less than that of formaldehyde, because of the slow evolution of gas.

Acrolein (acrylaldehyde) is an extremely irritating gas, used as a fumigant, aquatic herbicide, and "tear gas." The vapor causes lacrimation and upper respiratory tract irritation, which may lead to laryngeal edema, bronchospasm, and delayed pulmonary edema. The consequences of ingestion are essentially the same as those which follow ingestion of formaldehyde (see above). Contact with the skin may cause blistering.

Sulfur dioxide is a highly irritant gas, so disagreeable that persons inhaling it are usually warned to seek uncontaminated air as soon as possible. However, laryngospasm and pulmonary edema have occurred occasionally, leading to severe respiratory distress and death. It is sometimes a cause of asthma in occupationally exposed persons, even when air concentrations are low.

Sulfuryl fluoride has been used extensively for structural fumigation. Although use experience has generally been good, some fatalities have occurred when fumigated buildings have been prematurely reentered by unprotected individuals. Manifestations of poisoning have been nose, eye, and throat irritation, weakness, nausea, vomiting, dyspnea, cough, restlessness, muscle twitching, and seizures. Renal injury may induce proteinuria and azotemia.

Carbon disulfide vapor is only moderately irritating to upper respiratory membranes, but it has an offensive "rotten cabbage" odor. Acute toxicity is due chiefly to effects on the central nervous system. Inhalation of high concentrations for short periods has caused headache, dizziness, nausea, hallucinations, delirium, progressive paralysis and death from respiratory failure. More prolonged exposure to lesser amounts has lead to blindness, deafness, paresthesia, painful neuropathy, and paralysis. Long-term occupational exposures have been shown to accelerate atherosclerosis, leading to ischemic encephalopathy, myocardiopathy, and gastrointestinal dysfunction. Toxic damage to the liver and kidneys may result in severe functional deficits of these organs.

Phosphine gas is only slightly irritating to the respiratory tract, but is at least as toxic systemically as hydrogen cyanide. It is slowly released into treated produce or storage spaces by hydrolysis of solid aluminum phosphide (phostoxin). Mechanisms of toxicity are not well understood. The principal manifestations of poisoning are fatigue, nausea, headache, dizziness, thirst, cough, shortness of breath, paresthesia, and jaundice. Pulmonary edema is a common cause of death. Odor is said to resemble that of decaying fish.

Hydrogen cyanide gas causes poisoning by inactivating cytochrome oxidase, the final enzyme essential to mammalian cellular respiration. The cells of the brain appear to be the most vulnerable to cyanide action. Unconsciousness and death may occur immediately following inhalation of a high cyanide concentration, respiratory paralysis being the principal mechanism. Lesser exposures cause a constriction and numbness in the throat, stiffness of the jaw, salivation, nausea, vomiting, dizziness, and apprehension. Worsening of the poisoning is manifest as violent tonic or clonic convulsions. Trismus and opisthotonos occur. Paralysis follows seizure activity. Incontinence is characteristic. The skin remains pink. Fixed, dilated pupils, bradycardia, and irregular gasping respiration (or apnea) are typical of profound poisoning. The heart often continues to beat after breathing has stopped. A bitter almond odor to the breath or vomitus may be a clue to poisoning, but not all individuals are able to detect this odor. Similar color of the retinal arteries and veins may be a useful sign of cyanide poisoning: it is due to failure of reduction of hemoglobin as blood perfuses poisoned tissues.

Acrylonitrile is biotransformed in the body to hydrogen cyanide. Toxicity and mechanisms of poisoning are essentially the same as have been described for cyanide, except that acrylonitrile is irritating to the eyes and to the upper respiratory tract.

CONFIRMATION OF POISONINGS BY FUMIGANTS

Naphthalene is converted mainly to alpha naphthol in the body and promptly excreted in conjugated form in the urine. Alpha naphthol can be measured by gas chromatography.

Many **halocarbons** can be measured in blood by gas chromatographic methods, some using head space techniques. Some can be measured in the expired air as well.

Methylene chloride is converted to carbon monoxide in the body, generating carboxyhemoglobinemia, which can be measured by clinical laboratories.

Paradichlorobenzene is metabolized mainly to 2,5-dichlorophenol, which is conjugated and excreted in the urine. This product can be measured chromatographically.

Methyl bromide yields inorganic bromide in the body; the anion is slowly excreted in the urine (half-life in the body is about 12 days). The serum from persons having no exceptional exposure to bromide usually contains less than 1 mg bromide ion per 100 ml. The possible contributions of medicinal bromides to elevated blood content and urinary excretion must be considered, but if methyl bromide is the exclusive source, serum bromide exceeding 5 mg per 100 ml probably means some absorption, and 15 mg per 100 ml is consistent with symptoms of acute poisoning. Inorganic bromide is considerably less toxic than methyl bromide; serum concentrations in excess of 150 mg per 100 ml occur commonly in persons taking inorganic bromide medications.

In some European countries, blood bromide concentrations are monitored routinely in workers exposed to methyl bromide. Blood levels over 3 mg per 100 ml are considered a warning that personal protective measures must be improved. A bromide concentration over 5 mg per 100 ml requires that the worker be removed from the fumigant-contaminated environment until blood concentrations decline to less than 3 mg per 100 ml.

Carbon disulfide can be measured in urine by gas chromatography, but the test is not generally available. A qualitative test for carbon disulfide metabolites in urine (based on their reducing properties) is used for monitoring occupational exposure (Djuric D., N. Serducki, and I. Burkes. Iodine-azide test on urine of persons exposed to carbon disulfide. *Brit. J. Indus. Med.*, 22:321-3, 1965).

Cyanide ion from cyanide itself or acrylonitrile can be measured in whole blood and urine by an ion-specific electrode or by colorimetry. The upper limit in whole blood among nonexposed nonsmokers is about 0.02 mg per liter; it is 0.04 mg per liter in smokers. Symptoms may appear at levels above 0.10 mg per liter. Urine cyanide is usually less than 0.30 mg per liter in nonsmokers, but as much as 0.80 mg per liter in smokers. Thiocyanate, the metabolite of cyanide, can also be measured in blood and urine. It is usually present in plasma at levels less than 4 mg per liter in non-smokers, but up to 12 mg per liter in smokers. Urine thiocyanate is usually less than 4 mg per liter in nonsmokers, but may be as high as 17 mg per liter in smokers.

A serum fluoride concentration of 0.5 mg per liter was measured in one fatality from **sulfuryl fluoride** fumigation. Serum fluoride in persons not exceptionally exposed rarely exceeds 0.1 mg per liter.

There are no practical tests for absorbed alkyl oxides, aldehydes, or phosphine that would be helpful in diagnosis of poisoning.

Large industrial concerns sometimes monitor human absorption of halocarbons by analysis of expired air. Similar technology is available in some departments of anesthesiology. These analyses are rarely needed to identify the offending toxicant, because this is known from the exposure history. In managing difficult cases of poisoning, however, it may be helpful to monitor breath concentrations of toxic gas to evaluate disposition of the fumigant. Testing of the urine for protein and red cells is needed to detect renal injury. Free hemoglobin in urine most likely reflects hemolysis, as from naphthalene. Elevations of alkaline phosphatase, lactate dehydrogenase (LDH), serum GOT, ALT, AST, and certain other enzymes are sensitive indices of insult to liver cells. More severe damage increases plasma concentrations of bilirubin. The chest x-ray may be used to confirm the occurrence of pulmonary edema. Electromyography may be useful in evaluating peripheral nerve injury. Sperm counts may be appropriate for workers exposed to dibromochloropropane and ethylene dibromide.

Some occupational health agencies now urge periodic neurologic and neuropsychologic testing of workers heavily exposed to fumigants and solvents to detect injury to the nervous system as early as possible. This would be particularly desirable in the case of exposures to such agents as methyl bromide and carbon disulfide which have well documented chronic neurotoxic effects.

TREATMENT OF POISONINGS BY FUMIGANTS

1. **FLUSH** contaminating fumigants from the skin and eyes with copious amounts of water or saline for at least 15 minutes. Some fumigants are corrosive to the cornea and may cause **BLINDNESS.** Specialized medical treatment should be obtained promptly following removal of toxicant by copious flushing with clean water. Skin contamination may cause **BLISTERING** and deep chemical burns. Absorption of some fumigants across the skin may be sufficient to cause systemic poisoning in the absence of fumigant inhalation. For all these reasons, decontamination of eyes and skin must be **IMMEDIATE** and **THOROUGH.**
2. **REMOVE** victims of fumigant inhalation to **FRESH AIR** immediately. Even though initial symptoms and signs are mild, keep the victim quiet, in a semi-reclining position. Minimum physical activity limits the likelihood of pulmonary edema.

3. If victim is not breathing, clear the airway of secretions and **RESUSCITATE** with positive pressure oxygen apparatus. If this is not available, use chest compression to sustain respiration. If victim is pulseless, employ cardiac resuscitation.
4. If **PULMONARY EDEMA** is evident, there are several measures available to sustain life. Medical judgment must be relied upon, however, in the management of each case. The following procedures are generally recommended:
    - A. Put the victim in a **SITTING** position with a backrest.
    - B. Use intermittent and/or continuous positive pressure **OXYGEN** to relieve hypoxemia. (Do not give oxygen at greater concentrations or longer periods than necessary, because it may exaggerate the fumigant injury to lung tissue. Monitor arterial $p0_2$.)
    - C. Slowly administer **FUROSEMIDE**, 40 mg, or **SODIUM ETHACRYNATE**, 50 mg, intravenously, to reduce venous load by inducing diuresis. Consult package insert for additional directions and warnings.
    - D. Administer **MORPHINE** in small doses (5–10 mg), slowly, intravenously, to allay anxiety and promote deeper respiratory excursions.
    - E. Administer **AMINOPHYLLINE** (0.25–0.50 gm) slowly, intravenously. Consult package insert.
    - F. Digitalization may be considered, but there is a serious risk of arrhythmias in an anoxic and toxic myocardium.
    - G. **TRACHEOSTOMY** may be necessary in some cases to facilitate aspiration of large amounts of pulmonary edema fluid.
    - H. Epinephrine, atropine, and expectorants are generally not helpful, and may complicate treatment.
    - I. Watch for **RECURRENT PULMONARY EDEMA**, even up to 2 weeks after the initial episode. Limit victim's physical activity for at least 4 weeks. Severe physical weakness usually indicates persistent pulmonary injury. Serial pulmonary function testing may be useful in assessing recovery.
5. Combat **SHOCK** by placing victim in the Trendelenburg position and administering plasma, whole blood, and/or electrolyte and glucose solutions intravenously, with great care, to avoid pulmonary edema. Central venous pressure should be monitored continuously. Vasopressor amines must be given with great caution, because of the irritability of the myocardium.
6. Control **CONVULSIONS**. Seizures are most likely to occur in poisonings by methyl bromide, hydrogen cyanide, acrylonitrile, phosphine, and carbon disulfide.
    - A. Establish pulmonary gas exchange at the best possible level by administering **OXYGEN** by continuous positive pressure ventilation.

B. In poisoning by **CYANIDE** and **ACRYLONITRILE**, proceed directly with **ANTIDOTAL** therapy (see below paragraph 11E).

C. Control convulsions caused by other agents with careful IV injection of **DIAZEPAM**, 5–10 mg in adults and children over 12 years, 0.25–0.40 mg/kg in children under 12 years. (See Chapter 3, TREATMENT, Section 4, p. 21.) Repeat dosage in 4–6 hours if necessary.

CAUTION: Be prepared to maintain pulmonary ventilation mechanically, and to manage hypotension and cardiac arrhythmias. Alternative or supplemental anticonvulsive therapy is discussed in the reference cited.

D. In methyl bromide poisoning, it may be necessary to give benzodiazepines or barbiturates orally for days or weeks after the poisoning to control involuntary motor activity. Consult package inserts for appropriate dosages.

7. If a **FUMIGANT LIQUID OR SOLID** has been **INGESTED** less than several hours prior to treatment, quantities remaining in the stomach must be removed as effectively as possible by gastric intubation, aspiration, and lavage, after all possible precautions have been taken to protect the respiratory tract from aspirated gastric contents.

A. Put in place a cuffed **ENDOTRACHEAL TUBE** prior to gastric intubation. Administer **OXYGEN**, using a mechanical ventilator if respiration is depressed.

B. Lavage the stomach with a slurry of **ACTIVATED CHARCOAL** in saline or water. Leave a volume of the slurry in the stomach with an appropriate dose of sorbitol as cathartic (for dosages, see Chapter 1, TREATMENT, Section 6, p. 8).

C. If treatment is delayed and if the patient remains fully alert, administer activated charcoal and sorbitol orally. For dosage, see Chapter 1, TREATMENT, Section 6, p. 8. Repeated administration of charcoal at half or more the initial dosage every 2–4 hours may be beneficial.

D. Do not give vegetable or animal fats or oils, which enhance gastrointestinal absorption of many of the fumigant compounds.

8. Intravenous infusions of **GLUCOSE** are valuable in limiting the hepatotoxicity of many substances. Monitor central venous pressure to avoid precipitating, or aggravating, pulmonary edema by fluid overload. The victim should be watched closely for indications of delayed or recurrent pulmonary edema, and for bronchopneumonia. Fluid balance should be monitored, and urine sediment should be checked regularly for indications of tubular injury. Measure serum alkaline phosphatase, LDH, ALT, AST, and bilirubin to assess liver injury.

9. **HEMOPERFUSION OVER ACTIVATED CHARCOAL** has been used in managing a case of carbon tetrachloride poisoning with apparent success. An extraction efficiency of about 80% was demonstrated for the system employed (Schwarzbeck, A. and Kosters, W., **Arch. Toxicol.**, 35:207-211, 1976). It is possible that other fumigant compounds would be effectively removed from blood by this method.

10. **EXTRACORPOREAL HEMODIALYSIS** may be needed to regulate extracellular fluid composition if renal failure supervenes. It is probably not very effective in removing lipophilic fumigant compounds from blood, but is, of course, effective in controlling extracellular fluid composition if renal failure occurs.

11. Certain **SPECIFIC MEASURES** are recommended in poisonings by particular fumigants (naphthalene, methyl bromide, carbon tetrachloride, hydrogen cyanide):

    A. **NAPHTHALENE** toxicosis caused by vapor inhalation can usually be managed simply by removing the individual to fresh air. Skin contamination should be removed promptly by washing with soap and water. Eye contamination should be removed by flushing with copious amounts of clean water. Irritation may be severe, and if it persists, should receive medical attention.

    a. If solid naphthalene has been **INGESTED** and retained less than several hours prior to treatment, and if the patient is fully alert, the stomach should be emptied by administration of Syrup of Ipecac, followed by several glasses of water. Dosage for adults and children over 12 years: 30 ml; dosage for children under 12 years: 15 ml. When vomiting subsides, give activated charcoal and sorbitol (see Chapter 1, TREATMENT, Section 6, p. 8). If the patient is obtunded or excited, do not give Ipecac, but take steps to protect the airway, then aspirate and lavage the stomach with a slurry of activated charcoal. Leave charcoal and sorbitol in the stomach before withdrawing the tube (see above reference). Repeated administration of charcoal every 2-4 hours may be beneficial.

    b. If treatment is delayed more than several hours, administer as much activated charcoal orally as the patient will tolerate. Include sorbitol in the charcoal slurry unless diarrhea has already commenced.

    c. Examine the plasma for evidence of hemolysis: a reddish-brown tinge. Examine the blood smear for "ghosts" and Heinz bodies. If present, monitor red blood cell count and hematocrit for anemia, urine for protein and cells. Measure direct- and indirect-reacting bilirubin in the plasma. Monitor fluid balance and blood electrolytes. If possible, monitor urinary excretion of naphthol to assess severity of poisoning and clinical progress.

d. If hemolysis is clinically significant, administer intravenous fluids to accelerate urinary excretion of the naphthol metabolite and protect the kidney from products of hemolysis. Use Ringer's-lactate or sodium bicarbonate to keep urine pH above 7.5. Consider use of mannitol, furosemide, or ethacrynic acid to promote diuresis. If urine flow declines, intravenous infusions must be stopped to prevent fluid overload. Institute hemodialysis. Consider charcoal hemoperfusion in tandem to extract naphthalene and end-products.

e. If anemia is severe, blood transfusions may be needed.

f. Hydrocortisone may be of some benefit if significant hemolysis is present.

B. If given very soon after life-threatening exposure to **METHYL BROMIDE** there may be some theoretical value in administering **DIMERCAPROL** (BAL) in vegetable oil intramuscularly. For adults, give 3-5 mg/kg q6h for 4 to 6 doses. Neither the effectiveness nor the safety of this treatment has been tested in methyl bromide poisoning.

CAUTION: DIMERCAPROL may cause troublesome side effects (hypertension, tachycardia, nausea, headache, paresthesia, pain, lacrimation, sweating, anxiety, and restlessness). Although usually not so severe as to preclude treatment, these effects may require antihistamine therapy.

C. For **CARBON TETRACHLORIDE** poisoning, several treatment measures have been suggested to limit the severity of hepatic necrosis. Neither effectiveness nor safety of any of these measures has been established.

a. Inhalation of oxygen at one or two atmospheres for 2 hours twice daily may have some value.

b. Oral administration of tocopherol (vitamin E) in oral doses of several hundred milligrams per day has been suggested on grounds of its action as a free radical scavenger.

c. Oral administration of N-acetyl cysteine (Mucomyst) may be worthwhile as a means of reducing free radical injury. Dilute the proprietary 20% product 1:3 in soda-pop, and give about 3 ml/kg body weight of the diluted solution as a loading dose. Give half of this dosage every 4 hours after the loading dose for a total of 17 doses. (This dosage schedule is used for acetaminophen poisonings.) Administration via duodenal tube may be necessary in a few patients who cannot tolerate Mucomyst.

d. Hemoperfusion over activated charcoal should be considered. It was apparently effective in one carbon tetrachloride poisoning. See Schwarzbeck, A. and Kosters, W. Arch. Toxicol., 35:207-211, 1976.

D. Mild poisonings by **CARBON DISULFIDE** inhalation may be managed best by no more than careful observation, even though sensory hallucinations, delirium, and behavioral aberrations can be alarming. Severe poisonings may require specific measures:

a. If manic behavior threatens the safety of the victim, **DIAZEPAM**, 5-10 mg in adults, 0.2-0.4 mg/kg in children, administered slowly, intravenously, may be helpful as a tranquilizer. Give as much as is necessary to achieve sedation. Do not give catecholamine-releasing agents such as reserpine and amphetamines.

b. In severe poisonings by carbon disulfide, pyridoxine hydrochloride (vitamin B6) may have some antidotal action against the neurotoxic effects. Its value is theoretical; neither effectiveness nor safety has been tested in carbon disulfide poisonings. The usual dosage in other poisonings (ISONIAZID) has been 5 gm in a 10% solution, given slowly intravenously, or included in a one liter intravenous solution of 5% glucose. When the victim can swallow, pyridoxine hydrochloride can be given orally in daily doses as high as 25 mg/kg body weight. There is probably little value, and possibly some hazard, in extending the treatment beyond one or two weeks.

E. Poisonings by **HYDROGEN CYANIDE** and **ACRYLONITRILE** gases or liquids are treated essentially the same as poisoning by cyanide salts. Because cyanide is so promptly absorbed following ingestion, treatment should commence with **PROMPT ADMINISTRATION OF ANTIDOTES**, deferring gastric evacuation (in ingestion poisonings) until antidotes have been administered.

If the victim is an **ADULT**:

a. Administer **OXYGEN** continuously. If respiration fails, maintain pulmonary ventilation mechanically.

b. Administer **AMYL NITRITE** (perles) by inhalation for 15-30 seconds of every minute, while a fresh solution of 3% sodium nitrite is being prepared.

c. As soon as solution is available, inject intravenously 10 ml of 3% **SODIUM NITRITE** solution over a 2-4 minute interval, keeping the needle in place.

CAUTION: MONITOR PULSE and **BLOOD PRESSURE** during administration of amyl nitrite and sodium nitrite. If systolic blood pressure falls below 80 mm Hg, slow or stop nitrite administration until blood pressure recovers.

d. Follow sodium nitrite injection with an infusion of 50 ml of 25% aqueous solution of **SODIUM THIOSULFATE** administered over a 10-minute period. Initial adult dose should not exceed 12.5 gm.

e. If symptoms persist or recur, treatment by sodium nitrite and sodium thiosulfate should be **REPEATED AT HALF THE DOSAGES** listed in paragraphs c and d.

f. Measure hemoglobin and methemoglobin in blood. If more than 50% of total hemoglobin has been converted to methemoglobin, **BLOOD TRANSFUSION** or exchange transfusion should be considered, because conversion back to normal hemoglobin proceeds slowly.

If the victim is a **CHILD**:

a. Give amyl nitrite, oxygen, and mechanical respiratory support as recommended for adults.

b. The following dosages of antidotes have been recommended by C.M. Berlin (*Pediatrics*, 46:793-796, 1970).

   i) Children over 25 kg body weight should receive adult dosages of sodium nitrite and sodium thiosulfate.

   ii) Children less than 25 kg body weight should first have two 3-4 ml samples of blood drawn and then, through the same needle, receive 10 mg/kg (0.33 ml/kg of 3% solution) of **SODIUM NITRITE** injected over a 2-4 minute interval. Following sodium nitrite, administer an infusion of 1.65 ml/kg of 25% **SODIUM THIOSULFATE** at rate of 3-5 ml per minute.

   iii) At this point, determine the hemoglobin content of the pretreatment blood sample. If symptoms and signs of poisoning persist or return, give supplemental infusions of sodium nitrite and sodium thiosulfate based on hemoglobin level, as presented in TABLE 2. These recommended quantities are calculated to avoid life-threatening methemoglobinemia in anemic children. They are aimed at converting approximately 40% of circulating hemoglobin to methemoglobin. If possible, monitor blood methemoglobin concentrations as treatment proceeds.

TABLE 2. *Recommended dosages of supplemental sodium nitrite and sodium thiosulfate based on hemoglobin level.*

Initial Hemoglobin Concentration gm/100 ml	Supplemental Volume of 3% Sodium Nitrite, ml/kg	Supplemental Volume of 25% Sodium Thiosulfate, ml/kg
14.0	0.25	1.25
13.0	0.21	1.05
12.0	0.17	0.85
11.0	0.13	0.65
10.0	0.09	0.45
9.0	0.05	0.25
8.0	0.00	0.00
7.0	0.00	0.00

Although various cobalt salts, chelates, and organic combinations have shown some promise as antidotes to cyanide, they are not generally available. None have been shown to surpass the nitrite-thoisulfate regimen in effectiveness.

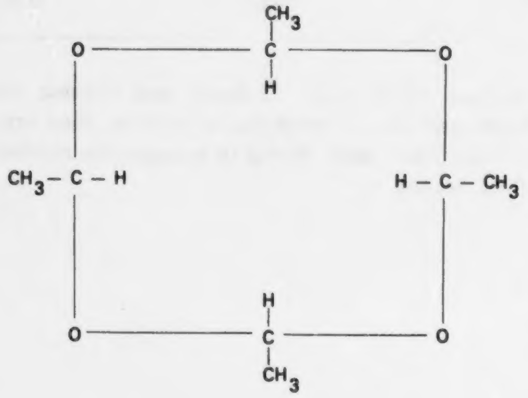
CHAPTER 15

MISCELLANEOUS PESTICIDES, SOLVENTS, AND ADJUVANTS

The following pest control agents are widely used and may occasionally pose a risk of human poisoning.

METALDEHYDE

CHEMICAL STRUCTURE



COMMERCIAL PRODUCTS

Antimilace, Bug-Geta, Cekumeta, Corry's Slug and Snail Death, Halizan, Metason, Namekil.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY METALDEHYDE

Metaldehyde is a 4-unit cyclic polymer of acetaldehyde long used to kill slugs and snails, which are attracted to it without the use of bait. Occasional poisonings of animals and children have resulted from ingestion of pellets intended as molluscicide, but tablets designed as fuel in smokeless lamps have more commonly been the agents responsible for human poisonings. The biochemical mechanism of poisoning is not known; acetaldehyde derived from depolymerization does not produce the dramatic neurologic symptoms and signs of metaldehyde poisoning.

Furthermore, acetaldehyde is not detectable in the blood or urine of metaldehyde-poisoned dogs.

Ingestion of a toxic dose is sometimes followed by vomiting due to gastric irritation. Within a few minutes to several hours following ingestion, salivation, flushing, abdominal cramps, vomiting, and generalized tremors occur; the latter may progress to violent tonic-clonic convulsions. Hyperthermia and tachycardia characterize some cases. Poisoned animals show tremors, ataxia, hyperesthesia, and salivation. Autopsy findings in fatal human poisonings indicate severe damage to liver cells and renal tubular epithelium. Metabolic acidosis may be an important factor leading to death.

CONFIRMATION OF METALDEHYDE POISONING

Chromatographic methods for measurement of metaldehyde in blood are described but are not generally available. Very little metaldehyde or acetaldehyde is excreted in the urine of metaldehyde-dosed dogs. Liver function tests and repeat urinalyses for protein and cells should be done to assess liver and kidney injury in poisoned patients.

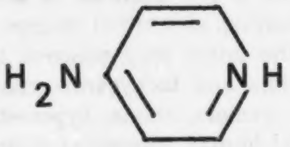
TREATMENT OF METALDEHYDE POISONING

Unless ingestion occurred more than several hours before treatment, ingested metaldehyde must be removed from the gut, preferably by gastric lavage and catharsis (see Chapter 1. TREATMENT, Section 6, p. 8). Activated charcoal may well be useful against metaldehyde. If seizures occur, sedative anticonvulsants must be administered (see Chapter 3, TREATMENT, Section 4, p. 21). Intravenous fluids, including glucose, should be given to protect the liver, support detoxication, and facilitate excretion. Add sodium bicarbonate to intravenous fluids to reverse metabolic acidosis. Fluid balance and electrolytes must be monitored carefully to avoid fluid overload if renal failure supervenes.

There is no specific antidote for metaldehyde poisoning. Hemodialysis is probably not effective in removing metaldehyde, but must be instituted if renal failure occurs. Effectiveness of hemoperfusion has not been tested.

4-AMINOPYRIDINE

CHEMICAL STRUCTURE



COMMERCIAL PRODUCTS

Avitrol, 4-Ap.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY AMINOPYRIDINE

4-Aminopyridine is a highly toxic white powder used as a bird repellant. (Only occasionally does it kill the poisoned bird: the cries and excited behavior of the affected bird cause others to take flight). It is usually added to grain baits in 0.5%-3.0% concentration, but 25% and 50% concentrates in powdered sugar are available. It is rapidly absorbed by the gut, less effectively across skin. The chief mechanism of toxicity is enhancement of cholinergic transmission in the nervous system. 4-Aminopyridine is rapidly metabolized and excreted. No human poisonings have occurred as a result of ordinary use, but the effects of ingestion of about 60 mg by each of two ill-advised adult humans have been reported. Both experienced immediate abdominal discomfort, nausea and vomiting, weakness, dizziness, and profuse diaphoresis. One patient suffered a tonic-clonic seizure and went into respiratory arrest. With supportive treatment, both recovered in 3 days. Poisoned laboratory animals commonly exhibit excitability, salivation, tremors, incoordination, convulsions, and cardiac or respiratory arrest.

TREATMENT OF POISONING BY AMINOPYRIDINE INGESTION

Unless ingestion occurred more than several hours before treatment, the stomach must be emptied by intubation, aspiration, and lavage with a slurry of activated charcoal, following placement of cuffed endotracheal tube (see Chapter 1, TREATMENT, Section 6, p. 8). Induced emesis may be a reasonable alternative if the patient is fully alert, but there is substantial risk of aspiration of gastric contents if convulsions or depressed consciousness level and reflexes occur before emesis. Gastric evacuation should be followed by administration of charcoal and sorbitol. If treatment is delayed, immediate oral administration of charcoal and sorbitol may represent optimal management. Seizures may require anticonvulsant medication (see Chapter 3, TREATMENT, Section 4, page 21). Dehydration should be treated with intravenous fluids if oral fluids cannot be retained.

CALCIUM CYANAMIDE

CHEMICAL STRUCTURE

$Ca{=}N-C{\equiv}N$

Calcium
Cyanamide

$H_2N-C{\equiv}N$

Hydrogen
Cyanamide

COMMERCIAL PRODUCTS

Cyanamide, nitrolime.

This synthetic compound is marketed as granules containing 44% calcium cyanamide, yielding 19.5% nitrogen. It is incorporated into soil to serve as fertilizer, fungicide, and herbicide. In contact with water, hydrogen cyanamide is released; the hydrolysis proceeds most rapidly under acid conditions. Hydrogen cyanamide is a solid with considerable vapor pressure. It has toxic properties totally different from those of cyanide, and it does not degrade to cyanide.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY CYANAMIDE

Calcium cyanamide is only moderately irritating to skin, but hydrogen cyanamide is severely irritating and caustic to skin and the inhaled gas is strongly irritating to mucous membranes.

The efficiency of dermal absorption of either form of cyanamide is not known; poisonings by this route have not been reported. Systemic poisonings have followed inhalation of hydrogen cyanamide and ingestion of the salt. Manifestations of poisoning are: flushing, headache, vertigo, dyspnea, tachycardia, and hypotension, sometimes progressing to shock. Because cyanamide is an inhibitor of acetaldehyde dehydrogenase, ingestion of alcohol exaggerates the symptoms. (A citrated form of cyanamide has been used in place of Antabuse in alcohol aversion therapy.)

TREATMENT OF CYANAMIDE POISONING

Skin contamination with either the calcium salt or the free form should be removed by washing with soap and water. Eye contamination should be removed by flushing the eyes with copious amounts of clean water. If skin or eye irritation persists, medical attention should be obtained promptly.

If large doses have been ingested recently, the stomach should be emptied with due care to protect the airway (Chapter 1. TREATMENT, Section 6, p. 8). If dosage was small or treatment is delayed, immediate oral administration of activated charcoal and sorbitol probably represents optimal management.

Treat hypotension or Antabuse-type reaction by placing the patient in Trendelenburg position, giving intravenous fluids, including plasma or blood, if needed, and, if necessary, vasopressor drugs parenterally.

Atropine is not antidotal.

SODIUM CHLORATE

CHEMICAL STRUCTURE

$$Na\,Cl\,O_3$$

COMMERCIAL PRODUCTS

Atratol, De-Fol-Ate, Dervan, Drexel Defol, Drop-Leaf, Fall, Harvest-Aid, Klorex, KM, Kusatol, Tumbleaf.

Sodium chlorate is used in agriculture as a defoliant, nonselective contact herbicide, and semipermanent soil sterilant. Because of its explosive nature, it must be formulated with water-soluble fire retardant material, such as sodium metaborate, soda ash, magnesium chloride, or urea. It is usually applied in water solution.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY SODIUM CHLORATE

Sodium chlorate is irritating to skin, eyes, and mucous membranes of the upper respiratory tract. Dermal absorption is slight. Even though gastrointestinal absorption is also inefficient, severe poisoning, sometimes fatal, follows ingestion of a toxic dose, said to be several grams in the adult human. Onset of symptoms is sometimes delayed as much as twelve hours. Excretion is chiefly in the urine. The principal mechanisms of toxicity are: hemolysis, methemoglobin formation, cardiac arrhythmia (partly secondary to hyperkalemia), and renal tubular injury. The irritant action on the gut causes nausea, vomiting, abdominal pain, and diarrhea. Hypotension may progress to shock. Cyanosis and dyspnea are prominent if hemolysis and methemoglobinemia are severe. Lumbar pain, proteinuria, hemoglobinuria, oliguria, and azotemia result from renal injury. Plasma and urine are dark brown from presence of free hemoglobin and methemoglobin. Release of potassium from red cell destruction results in hyperkalemia; this may be severe enough to cause life-threatening cardiac conduction defects. The liver is often enlarged and tender. Anoxemia may lead to convulsions. Death may be the result of shock, anoxemia, heart failure, or disseminated intravascular coagulation.

There are no widely available tests for chlorate specifically. Dark brown staining of the plasma and urine indicates the action of a strong oxidizing agent on hemoglobin.

TREATMENT OF CHLORATE POISONING

1. Skin contamination should be removed immediately by washing with soap and water. Medical attention should be sought if irritation persists.
   Eye contamination should be removed by flushing with copious amounts of clean water, then specialized medical attention should be obtained promptly, because irritant action may be severe.
2. If sodium chlorate has been ingested within several hours prior to treatment, put in place a cuffed endotracheal tube to protect the airway, then intubate the stomach, and lavage with a slurry of activated charcoal (Chapter 1, TREATMENT, Section 6, p. 8). After the lavage, instill 200 ml of 5% sodium bicarbonate containing 2-5 gm of **SODIUM THIOSULFATE** to decompose any remaining chlorate. Sorbitol should be administered if diarrhea has not already commenced.
3. Give **OXYGEN**. If respiration is depressed, maintain pulmonary ventilation with intermittent positive pressure breathing apparatus.
4. **SODIUM THIOSULFATE** intravenous infusion is an apparently successful antidote against absorbed sodium chlorate. Infuse 2-5 gm dissolved in 200 ml of 5% sodium bicarbonate over 60-90 minutes.
5. Monitor blood pressure, fluid balance, blood electrolytes, BUN, methemoglobin, and bilirubin, also urine protein, cells and free hemoglobin content, and ECG. Widening of the QRS complex and prolongation of the PR interval indicate hyperkalemic cardiac toxicity.
6. **MILK** may be helpful in relieving the pain of gastric irritation.
7. Administer **INTRAVENOUS FLUIDS** to sustain chlorate excretion. Maintain urine pH in the alkaline range by addition of sodium bicarbonate to the infusion fluid. Monitor urine production closely, so that intravenous fluids can be slowed or discontinued if renal failure occurs. **BLOOD TRANSFUSION** may be needed if hemolysis and methemoglobinemia are severe.
8. **HEMODIALYSIS** may be life-saving in severe poisoning. It is effective in removing chlorate from the blood, provides a means to

control hyperkalemia, and makes possible the control of extracellular fluid volume and composition while renal function remains impaired.

9. Administration of methylene blue to reverse methemoglobinemia may be considered if as much as 25–30% of hemoglobin is converted, even though use of this agent in chlorate poisoning has not proven beneficial in the past. Give intravenously 0.1 ml/kg body weight of a 1% solution over a period of at least 10 minutes. An increase in blood pressure, nausea, and dizziness may occur, but these effects are usually transient.

CREOSOTE

Creosote is obtained by distillation of the tar formed by heating wood or coal in the absence of oxygen. It is purified by extraction into oils. Creosote from wood consists mainly of guaiacol (methoxy phenol) and cresol (methyl phenol). Coal-derived creosote contains, in addition, some phenol, pyridine, and pyridinol. Creosote is extensively used as a wood preservative, usually by high-pressure impregnation of lumber. It has also been used as an animal dip and disinfectant.

Creosote is irritating to skin, eyes, and mucous membranes. Workers in contact with technical creosote or with treated timbers sometimes develop skin irritation, vesicular or papular eruptions, dermal pigmentation, and occasionally gangrene and skin cancer. Photosensitization has been reported. Eye contamination has resulted in conjunctivitis and keratitis, sometimes resulting in corneal scarring. The constituents of creosote are efficiently absorbed across the skin, but systemic poisonings following dermal absorption have occurred very rarely. Absorption of ingested creosote from the gut occurs promptly, and there may be significant absorption of vapor by the lung. Conjugates of absorbed phenolic constituents are excreted mainly in the urine. Acute toxic effects are similar to those of phenol, but toxicity is somewhat less. Irritation of the gastrointestinal tract, toxic encephalopathy, and renal tubular injury are the principal effects. A chronic toxicosis from continuing gastrointestinal absorption (creosote used medicinally) has been described, consisting of gastroenteritis and visual disturbances.

Manifestations of acute systemic poisoning are salivation, vomiting, dyspnea, headache, dizziness, loss of pupillary reflexes, cyanosis, hypothermia, convulsions, and coma. Moderate hypotension may progress to shock; vascular collapse is the usual cause of death, although respiratory depression may well be contributory. The presence of phenolic oxidation products imparts a dark, smoky color to the urine. If there is suspicion of poisoning, addition of a few drops of ferric chloride solution to the urine yields a violet or blue color indicating the presence of phenolic compounds.

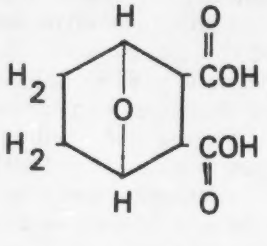
TREATMENT OF CREOSOTE POISONING

1. Stringent measures should be taken to avoid contamination of skin or eyes and inhalation of vapor. Skin contamination should be promptly washed off with soap and water. Contamination of the eyes should be removed by washing with copious amounts of water, then specialized medical attention should be obtained promptly because corneal injury may be severe.
2. If a significant amount of creosote has been ingested and the patient is alert and able to swallow, immediately administer a slurry of activated charcoal by mouth (for dosage, see Chapter 1, TREATMENT, Section 6, p. 8). Further efforts to limit absorption depend on whether there has been corrosive injury to the esophagus. If pharyngeal redness and swelling are evident, neither induced emesis or gastric lavage are advisable: emesis will re-expose the esophagus to the creosote, and a gastric tube may perforate the esophagus. If there is minimal evidence of pharyngeal injury, careful gastric intubation and lavage with activated charcoal may be undertaken after placement of a cuffed endotracheal tube to protect the airway. Sorbitol should be administered if diarrhea has not already developed in response to the creosote. Whether gastric lavage is accomplished or not, repeated administration of activated charcoal by mouth, at half or more the initial dose every 2–4 hours, may well be beneficial.
3. Maintain pulmonary ventilation mechanically with oxygen, if necessary.
4. Draw a blood sample to test for methemoglobinemia, to measure BUN and blood electrolytes, and to check for signs of liver injury (bilirubin, GOT, LDH, ALT, AST, and alkaline phosphatase). Test the urine for protein and cells, and for "smoky" phenolic excretion products.
5. Give fluids intravenously to correct dehydration and electrolyte disturbances. Include glucose to protect the liver and bicarbonate to relieve metabolic acidosis, as necessary. Monitor fluid balance carefully to signal discontinuation of intravenous fluids if renal failure occurs. Plasma or blood transfusion may be needed to overcome shock.
6. Monitor ECG to detect arrhythmias and/or conduction defects that may appear as manifestations of a toxic myocardiopathy.
7. Diazepam may be needed to control tremors or seizures. See Chapter 3, TREATMENT, Section 4, p. 21 for dosage.
8. Hemodialysis is not effective in accelerating disposition of phenol (or, presumably, creosote), but **HEMOPERFUSION** over charcoal probably is effective. This should be instituted in severe creosote poisonings.
9. Methemoglobinemia is rarely severe, but intravenous administration of 1% methylene blue may be considered if 25–30% of hemo-

globin is converted. Dose is 0.1 ml of 1% solution per kg body weight, given over no less than ten minutes. Nausea, dizziness, and a transient increase in blood pressure may occur.

ENDOTHALL

CHEMICAL STRUCTURE



COMMERCIAL PRODUCTS

Accelerate, Endothall Weed Killer, Aquathol, Des-i-cate, Endothall Turf Herbicide, Hydrothol, Herbicide 273.

As the free acid or as sodium, potassium or amine salts, endothall is used as a contact herbicide, defoliant, aquatic herbicide and algacide. It is formulated in aqueous solutions and granules at various strengths.

TOXICOLOGY AND MANIFESTATIONS OF POISONING BY ENDOTHALL

Endothall is irritating to skin, eyes, and mucous membranes. It is well absorbed across abraded skin and from the gastrointestinal tract. Recognized systemic toxic mechanisms in mammals are: 1) corrosive effect on the gastrointestinal tract (particularly from high concentrations of the free acid); 2) myocardiopathy and vascular injury leading to shock; and 3) central nervous system injury, causing convulsions and respiratory depression.

No human poisonings by endothall have been reported. There are no generally available tests to confirm absorption.

TREATMENT OF ENDOTHALL POISONING

1. Wash endothall from the skin with soap and water. Flush contamination from the eyes with copious amounts of clean water. Obtain medical attention if irritation of skin or eyes persists.
2. If endothall has been ingested, and if the patient is fully alert and not convulsing, prompt administration of **ACTIVATED CHARCOAL** may serve to limit toxicant concentration in the gastrointestinal tract. See Chapter 1, TREATMENT, Section 6, p. 8 for

dosage. Repeat charcoal administration every 2–4 hours at half or more the original dosage.

3. If there is no evidence of corrosive effect on pharyngeal tissues (or, presumably, on the esophagus), the stomach may be carefully intubated and lavaged with a slurry of activated charcoal, after all necessary measures have been taken to protect the airway from aspiration of vomitus (see Chapter 1, TREATMENT, Section 6, p. 8).
4. If there are indications of corrosive effects in the pharynx, gastric intubation should not be attempted because of the risk of esophageal perforation. Treatment procedures appropriate for ingestions of corrosives (strong acids and alkalis) may be necessary. A standard text of clinical toxicology should be consulted.
5. Oxygen should be given by mask. If respiratory drive is weak, pulmonary ventilation may have to be supported mechanically.
6. Monitor blood pressure closely. Infusions of plasma or blood may be needed to combat shock. Administer intravenous fluids to correct dehydration, stabilize electrolytes, provide sugar, and support mechanisms for toxicant disposition. Give vasoactive amines very carefully in light of myocardiopathy.
7. Seizures may require administration of diazepam and/or other anticonvulsants (see Chapter 3, TREATMENT, Section 4, p. 21).
8. It is not known whether hemodialysis or hemoperfusion would be effective in removing endothall from the blood. This option should be considered if the patient's condition deteriorates despite supportive care.

SYNERGISTS: PIPERONYL BUTOXIDE AND N-OCTYL BICYCLOHEPTENE DICARBOXIMIDE (MGK 264)

Synergists are chemical agents included in pesticide products to enhance the killing power of the active ingredients. The widely used insecticide synergists named above act by inhibiting the enzymatic degradation of pyrethrins, rotenone, N-methyl carbamates, and possibly some other insecticides. There is limited dermal absorption on contact. Inherent toxicity in mammals is low. Large absorbed doses may theoretically enhance the toxic hazard of the rapidly metabolized insecticides used today, although inhibition of human drug-metabolizing enzymes by these agents has not actually been demonstrated. Their presence in pesticide products to which humans are exposed does not change the basic approach to management of poisoning, except that some possibility of enhanced toxicity of the active insecticidal ingredients should be kept in mind.

SOLVENTS AND ADJUVANTS

Liquid materials in which pesticides are dissolved or the solids on which they are adsorbed (sometimes called carriers or vehicles), are chosen by producers to achieve stability of the active ingredient, convenience in handling and application, and maximum killing power following application. It is often the solvents and adjuvants which pesticide manufacturers choose that give their commercial products a competitive edge. For this reason, their inclusion in marketed products is usually proprietary information, not available to the general public except under emergency circumstances. If a poisoning emergency exists, pesticide companies will usually cooperate in supplying physicians with information needed to provide treatment. A direct request to the producer is necessary to secure this information.

Petroleum distillates are the most commonly used solvents for lipophilic pesticides. Most insecticides are lipophilic. The distillates are mixtures of aliphatic and aromatic hydrocarbons having low boiling points.

Sometimes specific hydrocarbons, such as toluene or xylene (strongly odiferous), are added to stabilize the solution of insecticide or make it more emulsifiable. Hydrocarbon-dissolved pesticides are usually diluted for application by adding measured amounts of water to form emulsions. Some chlorinated hydrocarbons may be present in particular technical mixtures. A strong odor lingering after application of a structural pest control spray is often due to the solvent rather than the active ingredient.

Less lipophilic active ingredients are sometimes dissolved in mixtures of alcohols, glycols, ethers, or various chlorinated solvents. It is possible that these enhance the dermal absorbability of some pesticides. Also, some solvents, for example, methanol and isopropanol, may represent a significant toxic hazard if swallowed in significant dosage.

Granular formulations utilize various clay materials which adsorb pesticide, retain it in more or less stable form until application, then desorb the material slowly into treated soil. There is some significant desorption when granules are in contact with human skin and very substantial desorption into gastrointestinal secretions if granules are swallowed. The clay materials themselves are not a toxic hazard.

Dusts are infrequently used today. Various forms of talc (silicate-carbonate particles) have been used in the past to adsorb pesticides for application to foliage. Particle sizes are such that these dusts are usually trapped in the upper respiratory mucous when inhaled. When the mucous is swallowed, the particles desorb pesticide into gastrointestinal secretions. Dust formulations may, therefore, release enough of some pesticides to cause systemic poisonings.

Stickers and spreaders (film extenders) are organic substances added to formulations to disperse pesticide over treated foliage surfaces and enhance adhesion thereto. The availability and persistence of residue on the leaf surfaces is thereby increased. Substances used include proteinaceous materials (milk products, wheat flour, blood albumin, gelatin), oils, gums, resins, clays, polyoxyethylene glycols, terpenes, and other viscid organics. Some also include sulfated alcohols, fatty acid esters, alkyl and petroleum sulfonates. For persons exposed in the course of formulation or application of pesticides, these adjuvants probably add little or no toxic hazard to that inherent in the active pesticidal ingredients.

Emulsifiers serve to stabilize water-oil emulsions formed when water is added to technical hydrocarbon concentrates. Chemically, they are detergent-like (one part of the molecule lipophilic, the other hydrophilic). Long-chain alkyl sulfonate ethers of polyethylene glycol and polyoxyethylene oleate are exemplary emulsifiers. They have low inherent mammalian toxicity, and their presence probably has little effect on the overall toxicity of formulated products which include them.

Penetrants facilitate the transfer of herbicide from foliage surface to the interior tissues. Some are lipids while others are detergent (surfactant) in nature. Substances used include heavy petroleum oils and distillates, polyol fatty acid esters, polyethoxylated fatty acid esters, aryl alkyl polyoxyethylene glycols, alkyl amine acetate, alkyl aryl sulfonates, polyhydric alcohols, and alkyl phosphates. Some of these are eye and skin irritants, and may account for the irritant effects of particular herbicide formulations whose active ingredients do not have this property.

Safeners are substances added to mixtures of fertilizers with pesticides (commonly herbicides) to limit the formation of undesirable reaction products. Some substances used are: alcohol sulfates, sodium alkyl butane diamate, polyesters of sodium thiobutane dioate, and benzene acetonitrile derivatives. Some are moderately irritating to the skin and eyes. Systemic toxicities are generally low.

Anticaking agents are added to granular and dust formulations to facilitate application by preventing cakes and clumps. Among several products used are the sodium salt of mono- and di-methyl naphthalene sulfonate, and diatomaceous earth. Diatomaceous earth has little adverse effect except a drying action on the skin. Methyl naphthalenes are said to be skin irritants and photosensitizers; whether their derivatives have this effect is not known.

TREATMENT CONSIDERATIONS

Petroleum distillates are mineral hydrocarbons which undergo limited absorption across the gut. In general, clinical toxicologists do not recommend induced emesis or gastric lavage in treating ingestions of these materials, because of the serious risk of hydrocarbon pneumonitis if even tiny amounts of the liquid are aspirated into the lung.

However, this injunction against emptying the stomach must be set aside when the petroleum distillate is a vehicle for toxic pesticides in significant concentration. Preferably, a cuffed endotracheal tube should be put in place before the stomach is aspirated and lavaged with a slurry of activated charcoal (Chapter 1, TREATMENT, Section 6, p. 8). If this protection is not available, all possible precautions should be taken (head down position, frequent aspiration of pharynx) to minimize the likelihood of aspiration of hydrocarbon into the respiratory tract. Rapid respiration, cyanosis, tachycardia, and low-grade fever are the usual indications of frank hydrocarbon pneumonitis. If these occur within 6-8 hours of gastric lavage, hospitalization is usually indicated. Within a few hours following gastric evacuation, a chest x-ray should be taken to detect or confirm signs of pneumonitis, the urine should be examined for protein, sugar, acetone, casts, and cells, and an ECG should be examined for arrhythmias and conduction defects. Mechanically assisted pulmonary ventilation with pure oxygen may be required. Hydrocarbon pneumonitis is sometimes fatal; survivors usually require several weeks for full recovery.

The presence of chlorinated solvents in some formulations may add significantly to the toxic hazard, particularly if the product is ingested. Certain adjuvants are irritants to skin, eyes, and mucous membranes, and may account for irritancy of some products whose active ingredients do not have this effect. With these exceptions, however, the presence of adjuvants in most finished pesticide products probably does not enhance or reduce systemic mammalian toxicity to any great extent.

CHAPTER 16

INDEX TO PESTICIDE POISONINGS BY SYMPTOMS AND SIGNS

Presented in this chapter are lists of pesticides reported to have caused particular symptoms and signs, or combinations thereof, in poisoned individuals. The lists may on occasion direct the attention of health professionals to possible toxic causes of the various disease manifestations, prompting inquiry into likelihood of exposure to the listed chemicals. If certain agents appear suspect, inquiry can then be made into the presence of additional manifestations typical of poisoning by those substances.

The limitations of this approach to diagnosis must be understood. First, all manifestations of illness have multiple causes, pesticidal and nonpesticidal. Second, there are no specific symptoms or signs that are invariably present in poisonings by particular pesticides. Third, many poisonings are characterized by unexpected manifestations.

Finally, it is evident that neither route of exposure nor dosage of pesticide is taken into account in this listing. For example, effects of high-dose ingestion are not distinguished from effects of relatively low-dose dermal absorption, nor are topical effects distinguished from systemic dermal manifestations. Clearly, the lists of pesticides can only be regarded as *clues* to prompt further inquiry by the interviewing professional.

The term manifestation means either symptom or sign. The word "poisoning" is used loosely in these headings to include topical as well as systemic effects. Pesticides which are relatively consistent in causing particular manifestations are listed in the middle column, headed "Characteristic of These Poisonings." Agents that have caused various conditions with less consistency, or are less prominent features of poisoning, are listed in the right-hand column, headed "Occurs in These Poisonings." Obviously, the distinction is not clear-cut.

Some symptoms (malaise, fatigue, dizziness) occur so commonly in poisoned individuals that they have little or no value in differential diagnosis, and are therefore not included in these tables.

SYSTEM	MANIFESTATION	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
General	Breath odor of:		
	Garlic	Arsenic Phosphorus Phosphides Phosphine	Thiram
	Bitter almonds	Cyanide	
	Rotten cabbage	Carbon disulfide	

—Continued

SYSTEM	MANIFESTATION	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
	Rotten egg Peanuts	Sulfur Pyriminyl	
	Hypothermia	Creosote Norbormide	
	Hyperthermia (fever, pyrexia)	Nitrophenols Pentachlorophenol	Borate Thallium Metaldehyde Inorganic arsenicals Chlorophenoxy compounds Cadmium dusts Naphthalene
	Chills	Phosphine Arsine	
	Hot sensations	Nitrophenols Chlordimeform	Pentachlorophenol
	Myalgia	Paraquat Chlorophenoxy compounds	
	Thirst	Pentachlorophenol Nitrophenols Inorganic arsenicals Phosphorus Phosphides Phosphine Sodium fluoride Cholecalciferol Aminopyridine	Borate Endothall
	Anorexia	Organophosphates Carbamate insecticides Nicotine Pentachlorophenol Hexachlorobenzene Chlordimeform Cholecalciferol	Halocarbon fumigants Nitrophenols Inorganic arsenicals Aminopyridine Pyriminil
	Alcohol intolerance	Thiram Calcium cyanamide	
	Sweet taste in the mouth	Chlordimeform	
	Metallic taste in the mouth	Inorganic arsenicals Organic mercury	
	Salty, soapy taste in the mouth	Sodium fluoride	
Skin	Irritation, rash, blistering, or erosion (without sensitization)	Copper, organotin, cadmium compounds Metam sodium Paraquat Diquat Sodium chlorate Phosphorus Sulfur Thiram	Pentachlorophenol Picloram Chlorophenoxy compounds Captan Rotenone Diethyltoluamide Creosote Fungicides and herbicides with irritant properties

—Continued

SYSTEM	MANIFESTATION	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
		Ethylene oxide Formaldehyde Acrolein Methyl bromide Eththylene dibromide Ethylene oxide Dibromochloropropane Dichloropropane Endothall Aliphatic acids	Petroleum distillate
	Flushing	Cyanamide Nitrophenols	Thiram plus alcohol
	Dermal sensitization	Propachlor Propargite Ethylene oxide	Anilazine Chlorothalonil Barban Captafol Formaldehyde
	Beefy red palms, soles	Borate	
	Urticaria		Fluoride
	Bullae	Liquid fumigants	Hexachlorobenzene
	Paresthesia (chiefly facial, transitory)	Fenvalerate Fluvalinate Cypermethrin Flucythrinate	
	Pallor	Organochlorines Fumigants Sodium fluoride Creosote	Coumarins Indandiones
	Cyanosis	Sodium chlorate Paraquat Cadmium dusts Sodium fluoroacetate Strychnine Crimidine Nicotine Chlorinated hydrocarbons	Organophosphates Carbamate insecticides Agents that cause shock, myocardiopathy, severe arrhythmias or convulsions.
	Yellow stain	Nitrophenols	
	Keratoses, brown discoloration	Inorganic arsenicals	
	Ecchymoses	Coumarins Indandiones	Phosphorus Phosphides
	Jaundice	Carbon tetrachloride Chloroform Phosphorus Phosphides Phosphine Paraquat Sodium chlorate	Inorganic arsenicals Diquat Copper compounds
	Excessive hair growth		Hexachlorobenzene

—Continued

SYSTEM	MANIFESTATION	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
	Loss of hair	Thallium	Inorganic arsenicals
	Loss of fingernails		Paraquat Inorganic arsenicals
	Brittle nails, white striations		Inorganic arsenicals Thallium
	Sweating, diaphoresis	Organophosphates Carbamate insecticides Nicotine Nitrophenols Pentachlorophenol Naphthalene Aminopyridine	Copper compounds
Eye	Conjunctivitis (irritation of mucous membranes, tearing)	Copper compounds Organotin compounds Cadmium compounds Metam sodium Paraquat Diquat Acrolein Chloropicrin Sulfur dioxide Naphthalene Formaldehyde Methyl bromide Ethylene oxide Endothall Toluene Xylene	Thiophthalimides Thiram Thiocarbamates Pentachlorophenol Chlorophenoxy compounds Chlorothalonil Picloram Creosote Aliphatic acids
	Tearing	Organophosphates Carbamate insecticides Chloropicrin Acrolein	Pentachlorophenol Pyrethrins
	Yellow sclerae	Nitrophenols	Agents that cause jaundice (see above under Skin)
	Keratitis	Paraquat	
	Ptosis	Thallium	
	Diplopia	Organophosphates Carbamate insecticides Nicotine	
	Photophobia		Organotin compounds
	Constricted visual fields	Organic mercury	
	Optic atrophy		Thallium
	Miosis	Organophosphates Carbamate insecticides	Nicotine (early)

—Continued

SYSTEM	MANIFESTATION	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
	Dilated pupils	Cyanide Fluoride	Nicotine (late)
	Unreactive pupils	Cyanide	
Nervous system	Headache	Organophosphates Carbamate insecticides Nicotine Inorganic arsenicals Organic mercury Cadmium compounds Organotin compounds Copper compounds Thallium Fluoride Borates Naphthalene Phosphine Halocarbon fumigants Creosote Diquat Cholecalciferol Cyanamide	Organochlorines Nitrophenols Thiram Pentachlorophenol Paraquat Diethyltoluamide
	Behavioral-mood disturbances (confusion, excitement, mania, disorientation, emotional lability)	Organic mercury Inorganic arsenicals Organotin compounds Thallium Nicotine Sodium fluoroacetate Diquat Cyanide Nitrophenols Pyriminil Aminopyridine Carbon disulfide Methyl bromide	Organophosphates Carbamate insecticides Pentachlorophenol Sodium fluoride Diethyltoluamide Organochlorines
	Nervous system depression, stupor, coma, respiratory failure, often without convulsions.	Organophosphates Carbamate insecticides Sodium fluoride Borate Diquat	Inorganic arsenicals Metaldehyde Sulfuryl fluoride Halocarbon fumigants Phosphorus Phosphides Phosphine Paraquat Chlorophenoxy compounds Diethyltoluamide Alkyl phthalates
	Convulsions (clonic-tonic), sometimes leading to coma.	Organochlorines Strychnine Crimidine Sodium fluoroacetate Nicotine Cyanide Acrylonitrile Metaldehyde	Nitrophenols Pentachlorophenol Inorganic arsenicals Organotin compounds Diquat Borate Sulfuryl fluoride Methyl bromide Chlorophenoxy compounds Organophosphates Carbamate insecticides Aminopyridine

—Continued

SYSTEM	MANIFESTATION	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
	Muscle twitching	Organophosphates Carbamate insecticides Nicotine Sulfuryl fluoride	Organic mercury Chlorophenoxy compounds
	Myotonia		Chlorophenoxy compounds
	Tetany, carpopedal spasms	Fluoride Phosphides Phosphorus	
	Tremor	Organic mercury Thallium Organophosphates Carbamate insecticides Nicotine Metaldehyde Borates	Pentachlorophenol Nitrophenols Thiram
	Incoordination (including ataxia)	Halocarbon fumigants Organophosphates Carbamate insecticides Carbon disulfide Nicotine Thallium	Organic mercury Organochlorines
	Paralysis, paresis, muscle weakness	Inorganic arsenicals Organophosphates Carbamate insecticides Nicotine	Organic mercury Diethyltoluamide
	Paresthesia of extremities	Inorganic arsenicals Organic mercury Sodium fluoroacetate Carbon disulfide Pyriminil Thallium	Pyrethroids (transitory)
	Hearing loss	Organic mercury	
Cardio-vascular system	Hypotension, shock	Phosphorus Phosphides Phosphine Sodium fluoride Sodium chlorate Borate Thallium Copper compounds Endothall Cyanamide	Inorganic arsenicals Nicotine (late) Creosote Alkyl phthalate Cycloheximide Formaldehyde Norbormide
	Hypertension	Thallium (early) Nicotine (early)	Organophosphates
	Cardiac arrhythmias	Sodium fluoroacetate Halocarbon fumigants Nicotine Sodium fluoride Ethylene oxide Sodium chlorate Pyriminil	Inorganic arsenicals Phosphorus Phosphides Phosphine Organochlorines Cyanide Acrylonitrile

—Continued

SYSTEM	MANIFESTATION	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
	Bradycardia (sometimes to asystole)	Cyanide Organophosphates Carbamate insecticides	Nicotine
	Tachycardia	Nitrophenols Pentachlorophenol Cyanamide	Metaldehyde Organophosphates
Respiratory system	Upper respiratory tract irritation: rhinitis, scratchy throat, cough	Naphthalene Paraquat Chloropicrin Acrolein Dichloropropene Ethylene dibromide Sulfur dioxide Sulfuryl fluoride Acrylonitrile Formaldehyde Cadmium dusts ANTU	Dry formulations of copper, tin, zinc compounds. Dusts of thiocarbamate and other organic pesticides. Chlorophenoxy compounds Aliphatic acids Rotenone
	Sneezing	Sabadilla	
	Runny nose	Pyrethrins Inorganic arsenicals Organophosphates Carbamate insecticides	(Irritants listed above)
	Pulmonary edema	Methyl bromide Phosphine Phosphorus Phosphides Ethylene oxide Ethylene dibromide Acrolein	Organophosphates Carbamate insecticides Paraquat Phosphides
	Pulmonary consolidation	Paraquat Cadmium dusts Methyl bromide	Diquat
	Dyspnea	Organophosphates Carbamate insecticides Nicotine Paraquat ANTU Cadmium dusts Cyanamide Sulfuryl fluoride Pentachlorophenol Methyl bromide Sulfur dioxide Chloropicrin	Nitrophenols Cyanide Creosote Pyrethrins
Gastrointestinal tract and liver	Nausea, vomiting commonly followed by diarrhea	Organophosphates Carbamate insecticides Nicotine Arsenicals Fluoride Cadmium compounds	Pentachlorophenol B. thuringiensis Cholecalciferol Thiram Many pesticides having some irritant property.

—Continued

SYSTEM	MANIFESTATION	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
		Organotin compounds Copper compounds Sodium chlorate Borate Cyanide Chlorophenoxy compounds Phosphorus Phosphides Phosphine Carbon disulfide Chloropicrin Halocarbon fumigants Endothall	
	Bloody diarrhea	Fluoride Paraquat Diquat Thallium Coumarins Indandiones Endothall Arsenicals	Phosphorus Phosphides Cycloheximide
	Abdominal pain	Organophosphates Carbamate insecticides Paraquat Diquat Nicotine Metaldehyde Fluoride Borate Phosphorous Phosphides Inorganic arsenicals Cadmium compounds Copper compounds Thallium Organotin compounds	Chlorophenoxy compounds Aliphatic acids Sodium chlorate Creosote Endothall Aminopyridine Coumarins Indandiones Fumigants (ingested) Cycloheximide
	Stomatitis	Inorganic arsenicals Paraquat Diquat Copper compounds	Thallium
	Salivation	Organophosphates Carbamate insecticides Nicotine Aminopyridine Sodium fluoride Cyanide Cadmium compounds	
	Ileus	Thallium Diquat	
	Constipation	Pyriminil	
Liver	Enlargement	Copper compounds Sodium chlorate Phosphine Carbon tetrachloride Cholorform	Inorganic arsenicals Hexachlorobenzene Other organochlorines

—Continued

SYSTEM	MANIFESTATION	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
	Jaundice—see section on "Skin"		
Kidney	Proteinuria, hematuria, sometimes leading to oliguria, acute renal failure with azotemia	Inorganic arsenicals Copper compounds Sodium fluoride Naphthalene Borate Nitrophenols Pentachlorophenol Sodium chlorate Sulfuryl fluoride Paraquat Diquat Arsine Ethylene dibromide	Cadmium compounds Phosphorus Phosphides Phosphine Chlorophenoxy compounds Creosote Organotin compounds
	Dysuria, hematuria, pyuria	Chlordimeform	
	Urinary retention	Pyriminil	
	Polyuria	Cholecalciferol	Fluoride
	Hemoglobinuria	Naphthalene Sodium chlorate Arsine	
	Wine-red urine (porphyrinuria)	Hexachlorobenzene	
	Smoky urine	Creosote	
	Glycosuria	Pyriminil	Organotin compounds
	Ketonuria	Pyriminil	Borate
Blood	Hemolysis	Naphthalene Sodium chlorate Arsine	Copper compounds
	Methemoglobinemia	Sodium chlorate Creosote	
	Hypoprothrombinemia	Coumarins Indandiones	Phosphorus Phosphides Carbon tetrachloride
	Hyperkalemia	Sodium chlorate Naphthalene Arsine	Sodium fluoride

—Continued

SYSTEM	MANIFESTATION	CHARACTERISTIC OF THESE POISONINGS	OCCURS IN THESE POISONINGS
	Hypocalcemia	Fluoride	Thallium Phosphorus Phosphides
	Hypercalcemia	Cholecalciferol	
	Carboxyhemoglobinemia		Methylene chloride
	Hyperglycemia	Pyriminil	Organotin compounds
	Ketoacidosis	Pyriminil	
	Anemia	Naphthalene Sodium chlorate Arsine Inorganic arsenicals	
	Leukopenia, thrombocytopenia	Inorganic arsenicals	
	Elevated LDH, GOT, GPT, alkaline phosphatase, ALT, AST enzymes	Carbon tetrachloride Chloroform Phosphine	Inorganic arsenicals Phosphorus Phosphides Phosphine Sodium chlorate Nitrophenols Pentachlorophenol Thallium Organochlorines Chlorophenoxy compounds
	Depressed RBC acetylcholinesterase and plasma pseudocholinesterase	Organophosphates	Carbamate insecticides
Reproductive system	Low sperm count	Dibromochloropropane	Kepone

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